Appendix

Study Protocol and SAP for: Georg M.N. Behrens, Lambert Assoumou, Geoffrey Liegeon, Andrea Antinori, Rafael Micán et al. **Integrase versus protease inhibitor therapy in advanced HIV disease: The Late Presenter Treatment Optimization (LAPTOP) Randomized Trial**

All documents are for the LAPTOP Study

1. **Study Protocol v1.5** (08 Jan 2019)
2. **Study Protocol v5.0** (11 March 2024)
3. **Statistical Analysis Plan (SAP) v0.3** (22.11.2023)

Changes in the protocol, which was initially approved by the ethics committee (UK), are summarized on page 2-13

Protocol v1.4 to v1.5 (UK only)

This amendment was only in the UK. EU territories initiated on Protocol v1.5 or later.

1. A change of vendor from Covance to ACM Global for the shipment and storage of resistance samples for deep sequencing. This change has also been incorporated into the patient information sheet and informed consent form. Updates to other addresses have also been incorporated.
2. Addition of a weight assessment at week 24 and 48 in the schedule of assessment table. This addition has been included due to scientific evidence that the IMPs used for the study may have a minor effect on patient's weight.
3. Section 6.1.3 required clarification regarding treatment switching
4. Update to one of the secondary outcomes which required additional wording regarding resistance mutations at baseline as patients may switch treatment due to resistance testing results or discontinue medication completely. Although this is not new, it should have been incorporated into the outcome in the previous versions of the protocol.

Protocol v1.5 to v2.0

Comparative table with description of change and rationale for change to the protocol from version 1.5 to version 2.0 (Substantial Amendment 2)

Change No.	Description of Change	Rationale for Change
1.	Study Synopsis- Treatment Arm 2 is referred to as the "comparator arm" to Treatment Arm 1.	This wording was added to ensure that the naming of treatment arm 2 is consistent with how it is described in the Development Safety Update Report.
2.	Section 1.2.1- "Urticaria" has been added as a new uncommon side effect of Biktarvy® and "Changes in Serum Creatinine" and "Changes in Billirubin" contains stability data of up to week 96 (previous data went up to week 48).	These changes reflect the updates contained in the latest version of the Reference Safety Information for Biktarvy® (02 April 2020)
3.	Section 5.1. Inclusion criteria 4b- Window for severe bacterial infection and CD4 cell count changed from "30 days" to "28 days"	This was changed to be consistent with the time window allowed for the use of historic test results (28 days) as screening results
4.	Section 5.1. Inclusion criteria 4c- Sentence changed from "Are asymptomatic with a CD4 cell count < 100/µL within 30 days" to "Any symptoms or no symptoms and must have a CD4 cell count < 100/µL within 28 days''	This sentence was modified because of feedback from several sites who commented that the wording in protocol version 1.5 was not clear. Time window changed from 30 days to 28 days for consistency

Change No.	Description of Change	Rationale for Change
5.	Section 5.1. Footnote added to the following: Inclusion criteria 2: "Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade haemoglobin based on the gender with which they identify (i.e. a transgender female should be graded using the female sex at birth hemoglobin laboratory values)"	This sentence was added to clarify the gender being collected for transgender participants.
6.	Section 5.1. Additional wording was added to the following footnote for: Inclusion criteria 3: "(severe or medically significant but not immediately life-threatening, see Appendix 2)"	The sentence in brackets was added to provide a definition for "grade 3 severity".
7.	Section 5.1. Footnote added to the following: Inclusion criteria 4b: "Study entry is defined as the start of the screening process"	This sentence was added to clarify what is meant by "study entry".
8.	Section 5.1. Inclusion criteria 4d) ii: The sentence has been modified to the following "Current OI treatment can have been discontinued prior to start of ART"	The modification was made to remove the following sentence" Current OI treatment must have been started ≤ 14 days prior to study entry"; this was reviewed and considered none- mandatory for a patient to be eligible for the study.
9.	Section 5.1. Inclusion criteria 5 added: "Have an entry HIV viral load > 1000 copies/mL"	This sentence was added to clarify that participants must have an entry HIV viral load > 1000 copies/mL to be eligible for the study
10.	Section 5.2 Exclusion criteria 1: Sentence modified to read the following "Any therapeutic ARV which commenced less than 2 weeks prior to screening and which	This sentence was modified to allow patients, who have been treated with ARV for other indications (such as patients infected with COVID-19) to still be eligible to enter the study, provided that their ARV commenced

Change No.	Description of Change	Rationale for Change
	study entry was taken for more than 48 hours"	less than 2 weeks prior to screening and was not taken for more than 48 hours
11.	The following changes have been made to Section 8- Pharmacovigilance: <u>Section 8.1 Definitions table</u>: The following has been removed from the definition of a SUSAR "in question set out: -in the case of a product with a marketing authorisation, in the SmPC for that product -in the case of any other investigational medicinal product, in the IB relating to the trial in questions" <u>Section 8.2:</u> Removal of the following paragraph "An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the study treatments. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP." <u>8.2.3 Collection and Follow up of Adverse Events</u> Removal of the sentence "AEs not already reported in the RSI for the study drugs will be considered unexpected." <u>8.2.4 Recording and Reporting of SAEs and SUSARs</u>	These changes have been made to ensure that the protocol is in line with the pharmacovigilance processes and procedures of the Sponsor.

Change No.	Description of Change	Rationale for Change
	Removal of "8.3 Serious Adverse Events (SAEs)" heading and addition of new subheading "8.2.4 Recording and Reporting of SAEs and SUSARs" Paragraph one modified to read the following "The SAE should be reported to the sponsor using the study Safety Event Reporting Form (SERF), within 24 hours of a member of the study team becoming aware of the event via e-mail to Safety@rokcservices.com or via the fax number provided on the SERF." Removal of subheading section "8.3.1 Recording and Reporting of SAEs and SUSARs" 8.8.3 Responsibilities Re-numbering of subheadings in this section and insertion of safety@rokcservices.com email address for safety reporting.	
12	Appendix 1- Study Flowchart. The following changes have been made to the schedule of assessments and assessment sub-notes: Physical examination (height and weight) to be carried out from screening through to week 48 visit. Previous schedule only required this at baseline, week 24 and week 48 visit. Urinalysis no longer required at baseline, week 4 and week 8 visits. Assessment sub note 1- The following text has been added: "The maximum time between screening visit and baseline visit is 28 days; however, participants should be invited for their baseline	These changes have been made to: a) Reflect any updates made to the Inclusion and Exclusion criteria of the protocol b) To define which historic test results can be used for screening c) To allow for the use of certain screening test results to be used as baseline results and to clarify which ones these are d) To address common questions which have been asked since the study commenced and to provide clarity on certain assessment criteria

Change No.	Description of Change	Rationale for Change
	visit as soon as reasonably possible in order to start their treatment. Only the following laboratory assessments are required for screening and historic (up to 28 days old) tests results may be used for screening: • HBV and HCV testing • TB test • CD4 & CD8 testing • Platelet count testing • Clinical chemistry (only creatinine, creatinine clearance, eGFR, potassium, sodium, ALT, AST is required) • Viral load testing • Resistance testing (the last resistance test carried out can be used)" "A serum pregnancy test is mandatory at the screening visit for women of childbearing potential" Urinary proteins has been removed from the above list. Assessment sub note 2 The following baseline visit sub note has been added "For baseline results, all screening tests carried out within 10 days before baseline can be used. This includes historic screening results, as long as they fall within the 10 day window before baseline. Screening data obtained more than 10 days from baseline, must be repeated at baseline" Assessment sub note 5 The following text has been added "If an ECG is not performed at screening, it must be performed by the time of the baseline visit."	

Change No.	Description of Change	Rationale for Change
	Assessment sub note 6 The following text has been added "For screening, test results 28 days prior to the screening visit can be used." Assessment sub note 7 The following text has been added "For screening, test results 28 days prior to the screening visit can be used. Patients can be randomised into the study without having the latent TB screening results available at randomisation" Assessment sub note 8 The following text has been added "If a HIV resistance test was done previously and results are available, the last resistance test carried out shall be considered." Assessment sub note 10 The following text in bold has been added: "Including: • Urinary creatinine* • Urinary glucose (dipstick test sufficient) * • Urinary proteins* • Albumin (can be obtained from 'spot' urine test) * • Nitrites (dipstick test sufficient) * • Albumin: Creatinine Ratio (ACR) and Protein: Creatinine Ratio (PCR) • Urinary phosphate • Beta-2 microglobulin • Leukocytes (dipstick test sufficient) Assessments should be performed as per local site procedure; however,	

Change No.	Description of Change	Rationale for Change
	assessments marked with an asterisk are mandatory for the study at and after baseline. Assessment sub note 11 In addition to some of the tests already marked with an asterix, the following assessments also now have asterixis: • RBC Count (indices MCV & MCH)* • WBC count (absolute)* • MCV* • MCH* • Monocytes* • Eosinophils* • Basophils* The following text has been added "Assessments that have been underlined are required at screening (results up to 28 days old can be used)." Assessment sub note 12 The following text in bold has been added "Assessments should be performed as per local site procedure; however, assessments marked with an asterisk are mandatory for the study at and after baseline. Assessments that have been underlined are required at screening (results up to 28 days old can be used." Assessment sub note 13 The following text in bold has been added "HIV RNA viral load-results obtained 28 days prior to screening can be used" Assessment sub note 18	

Change No.	Description of Change	Rationale for Change
	The following text has been added "If a urine pregnancy test is not possible, a serum pregnancy test can replace this." Assessment sub note 19 The description here has been modified to read "Weight is required at all visits, as detailed in the appendix 1, however height is only required at baseline."	
13.	Removal of subheading 13.7 from Protocol Version 1.5 which read: "2.1 Financial and other competing interests for the CI, PIs at each site and committee members for the overall trial management. The sponsor will identify and collect the following disclosure information: • Ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial • Commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company • Any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.''	This was removed as financial and competing interests is covered in the site agreements (PI Declaration section).

Protocol v2.0 to v4.0 (UK only)

Comparative table with description of change and rationale for change to the protocol from version 2.0 to version 4.0.

Please note version 3.0 was never fully approved in any territory due to an error in the document. V4.0 re-incorporates all approved changes made previously and also includes the following:

Change No.	Description of Change	Rationale for Change
3.	Changes made to reference the compliance with Clinical Trial Regulation (EU) No 536/2014 in the statements the CI, Sponsor, statistician, and PIs sign. Addition of EUCT number to title page.	Compliance with Clinical Trial Regulation (EU) No 536/2014
4.	Protocol summary: Number of sites and countries changed from 45 to 61, and 7 to 11, respectively.	Expansion of trial sites and territories is ongoing.
5.	Section 1.2.1: Therefore, in cases when needs *ART needs* to be initiated before genotypic testing results are available	Typographical error on in the background and rationale section
6.	Section 1.2.1, Section 7.1 and Section 7.7: Change to the language regarding the referenced RSI provided by the sponsor in	Changed to emphasize that the study team should refer to the particular SmPC provided and authorised as the RSI in the study, even if this is not the local country version or most current.
7.	Section 5.2: Exclusion Criteria: Removal of the requirement that forbidden concomitant medications should have been stopped at least 30 days ahead of baseline.	30 days was added initially at the start of the trial when there was less safety data available for Biktarvy, in particular, as it was not yet authorised when the protocol was written. Therefore, it was thought to exclude all contraindicated medication for 30 days as a safety precaution. However, it is now thought this is unnecessary and the sites should follow any recommendations in the SmPC.
8.	Section 5.2 and Appendix 1: A latent TB test may be performed. Previously a TB test will be performed	To clarify that the test is to confirm if latent TB is present. Additionally, TB testing has always been intended to be done in those patients in who it may be suspected. This wording has been changed to clarify that.

Change No.	Description of Change	Rationale for Change
9.	Removal of "Investigator Brochure" from the title of section 7.1	There is no Investigator Brochure used for the trial.
10.	Section 8.2.4 and Section 8.3.3.: 1. Additional text to state that details of reporter included on the Safety Event Report Form 2. Addition of text to mention the pharmacovigilance management plan (PVMP) will be used by the CI and sponsor in assessment of safety reporting	Addition in line with change to Sponsor's safety event reporting form to include the pharmacovigilance management plan (PVMP).
11.	Section 8.2.4 Recording and Reporting of SAEs and SUSARs Statement made that the Sponsor will update the Eudrvigilance database.	Compliance with Clinical Trial Regulation (EU) No 536/2014
12.	Section 8.3.6 and Section 12 Addition of details regarding Endpoint committee review	An endpoint committee may be requested ahead of any data analysis required by the DSMB or the TSC.
13.	8.8 Development Safety Update Reports Statement of intent for the sponsor to submit a single safety report for both IMP	Compliance with Clinical Trial Regulation (EU) No 536/2014
14.	9.5 Interim analysis and criteria for the premature termination of the trial Statement that there are no specific trial stopping criteria	Compliance with Clinical Trial Regulation (EU) No 536/2014
15.	13.3 Regulatory Compliance Change to reflect the trial will be conduct in compliance with Clinical Trial Regulation (EU) No 536/2014	Compliance with Clinical Trial Regulation (EU) No 536/2014
16.	13.6 Data protection and patient confidentiality Updated to comply with the Clinical Trial Regulation (EU) No 536/2014	Compliance with Clinical Trial Regulation (EU) No 536/2014

Change No.	Description of Change	Rationale for Change
17.	Section 13.5: Change to the definition of serious breach and reporting timelines	The previously included strictly MHRA definition has hence been modified to include the Clinical Trial Regulation wording.
18.	Appendix 1: Study Flowchart Removal of "including urinary chemistry" after "Clinical Chemistry" in the description of this assessment	The words are superfluous as the actual tests required are described in the footnote 12 – removing them for clarity for the sites.
19.	Appendix 1: Change to the footnote 10 wording after the asterisk: regarding when assessments should be taken. Changing from "after baseline" to "at all visits required"	Changing this for clarity as it is ambiguous about whether urinalysis assessments should be done at all visits.
20.	Appendix 1: Additional wording to state that either urinary creatinine or ACR and PCR are mandatory, not both	As it is the ACR and PCR which are required, and these are calculated from the urinary creatinine, if the ACR and PCR are provided by the site directly and the site do not routinely also provide the urinary creatinine in lab reports, this is acceptable.
21.	Appendix 1: Change to clarify that, as CD4 and CD8 can be calculated from total lymphocytes and CD4% and CD8%, CD4 and CD8 count are not mandatory	CD4% and CD8% and lymphocytes are already mandatory.
22.	Appendix 1: Urinary nitrites are no longer mandatory	It is considered that urinary nitrites are not a necessary safety test that is needed.

Protocol v4.0 to v5.0 (EU only)

Comparative table with Description of Change and Rationale for change to the Protocol from Version 4.0 to Version 5.0.

Protocol v4.0 was submitted in the EU but subsequently updated to v5.0 during the approval process due to the requirement for updated data protection wording. V5.0 is the same as v4.0 in almost all aspects. V5.0 is the final version for EU territories.

Change No.	Description of Change	Rationale for Change
1.	Section 13.6: Additional wording to clarify how data is stored and processed at the end of the study, and in what format	Compliance with Clinical Trial Regulation (EU) No 536/2014

An Open-Label, Multi-Centre, Randomised Study to Investigate Integrase Inhibitor Versus Boosted Protease Inhibitor Antiretroviral Therapy for Patients with Advanced HIV Disease

-The Late Presenter Treatment Optimisation Study (LAPTOP)-

Version 1.5 dated 08 January 2019

SPONSOR: NEAT ID Foundation

Sponsor code: NEAT44

EudraCT: 2018-003481-13

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GCP Compliance Statement:
This trial will be conducted in compliance with the protocol, the principles that have their origin in the Declaration of Helsinki and all applicable regulatory requirements

SPONSOR AND CHIEF INVESTIGATOR SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the trial Sponsor:

Signature: _____ Date: ____ / _____ / _____

Name (print): _____

Chief Investigator:

Signature: _____ Date: ____ / _____ / _____

Name (print): _____

STATISTICIAN OR STUDY ANALYST SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Statistician or Study Analyst agrees to conduct the trial in compliance with the approved protocol, Statistical Principles for Clinical Trials, ICH E10 and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Statistician or Study analyst

Signature: _____ Date: ____ / _____ / _____

Name (print): _____

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the trial in accordance with ICH-GCP and the applicable regulatory requirements and with the approved protocol.

I agree to comply with the procedures for data recording/reporting

I agree to permit monitoring, auditing and inspection at this site and to retain all trial related essential documentation for the duration of the study as required according to ICH-GCP.

Principal Investigator:

Signature: _____ Date: ____ / _____ / _____

Name (print): _____

TABLE OF CONTENTS

KEY TRIAL CONTACTS

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FUNDING AND SUPPORT

FUNDERS/COLLABORATORS
Gilead Sciences, Inc. 333 Lakeside Drive Foster City CA 94404
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STUDY SYNOPSIS

Full Study Title	An Open-Label, Multi-Centre, Randomised Study to Investigate Integrase Inhibitor Versus Boosted Protease Inhibitor Antiretroviral Therapy for Patients with Advanced HIV-Disease
Short Title/Acronym	LAPTOP (The Late Presenter Treatment Optimisation Study)
Clinical Phase	IIIb
Trial Design	International, multi-centre, randomised, open-label, controlled study comparing two strategies for HIV-1 infected patients with advanced disease. Randomisation 1:1 into two arms, 48 weeks, stratified according to country and baseline CD4 cell count (<50 cells/µL, 50-199 cells/µL, or ≥200 cells/µL).
Name of Investigational Product	Treatment Arm 1 Bictegravir (50mg)/emtricitabine (200mg)/tenofovir alafenamide (25mg) [1 pill administered orally once daily for 48 weeks without regard to food] Treatment Arm 2 Darunavir (800 mg)/cobicistat (150 mg)/emtricitabine (200 mg)/tenofovir alafenamide (10mg) [1 pill administered orally once daily for 48 weeks with food]
Trial Participants Population	HIV-1 infected patients ≥ 18 years and ART-naïve prior to enrolment.
Planned Sample Size	440 (220 subjects per treatment arm)
Key Eligibility Criteria	Subjects who meet the following eligibility criteria: 1. Ability to understand and sign a written informed consent form (ICF) and must be willing to comply with all study requirements 2. ≥ 18 years 3. HIV-1 infected AIDS except active tuberculosis (TB) or cryptococcal meningitis with any CD4 cell count, or; severe bacterial infection (BI) and must have a CD4 cell count < 200/µL within 30 days prior to study entry, or; asymptomatic with CD4 cell count < 100/µL within 30 days prior to study entry and must have an entry HIV viral load > 1000 copies/mL, or; currently being treated for opportunistic infections (OI) 4. ART-naïve prior to study enrolment 5. Able to take oral medications 6. Willing to use acceptable methods of contraception
Treatment duration	48 weeks
Follow up duration	30 days
Formulation, Dose, Route of Administration	Subjects will be randomised in a 1:1 ratio into one of two treatment arms: Group 1 Integrase inhibitor containing regimen Bictegravir (50 mg)/emtricitabine (200 mg)/tenofovir alafenamide (25mg) [1 pill administered orally once daily without regard to food for 48 weeks] Group 2 Boosted protease inhibitor regimen

	Darunavir (800 mg)/cobicistat (150 mg)/emtricitabine (200 mg)/tenofovir alafenamide (10mg) [1 pill administered orally once daily with food for 48 weeks]	
Indication	ART-naïve HIV-1 infected patients	
Methodology	Eligible consented patients will be randomised in a 1:1 ratio	
Number of sites	Up to 45 sites, in up to 8 countries	
Objectives	**Primary** To demonstrate the non-inferiority of an INI containing regimen [bictegravir (B)/emtricitabine (F)/tenofovir alafenamide (TAF) QD] versus a boosted PI regimen [darunavir (D)/cobicistat (C)/emtricitabine (F)/tenofovir alafenamide (TAF) QD] in patients with advanced HIV infection.	**Secondary** To investigate the immunological and virological response, tolerability, resistance development, discontinuation of therapy due to tolerability, QOL and IRIS incidence.
Outcome Measures	**Primary** 1. Time to failure, as the first occurrence of specified virological or clinical reasons.	**Secondary** 1. Proportion of patients with HIV-RNA viral load < 50 copies/mL at week 24, 36, 48 2. HIV-1 drug resistance at confirmed virological failure (genotype) 3. Time to reach CD4 count > 200/µL 4. Proportion of patients with CD4 cell count <200 and < 350µL at week 4, 8, 12, 24, 36, 48 5. CD4/CD8 ratio at week 4, 8, 12, 24, 36, 48 6. Incidence of IRIS in the two arms through week 48 7. Incidence and duration of hospitalisation, rate of relapse of specific OI/BI through week 48 8. Safety and tolerability, measured by Grade 2, 3 and 4 signs and symptoms and laboratory toxicities through week 48 9. ART and OI/BI treatment changes and dose modifications due to toxicities and DDI with ART, and IRIS through week 48 10. Health care resource use, including total inpatient days and emergency room visits through week 48 11. QOL and functional status outcomes, including overall self-reported QOL and functional status compared in the two groups at week 48 12. Discontinuation or modification of study medication due to

		insufficient virological response, resistance mutations at baseline, or resistance mutation development before week 48

LIST OF ABBREVIATIONS

Acronym	Description
3TC	Lamivudine
ABC	Abacavir
ACTG	AIDS Clinical Trial Group
ADE	Adverse Drug Event
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
ANRS	Agence Nationale de Recherches sur le SIDA (National Agency for AIDS Research)
AR	Adverse Reaction
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
B/BIC	Bictegravir
BI	Bacterial Infection
BMD	Bone Mineral Density
C	Cobicistat
CA	Competent Authority
CDC	Centres for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Chief Investigator
CI	Confidence Interval
CRF	Case Report Form
CTA	Clinical Trial Authorisation
D/DRV	Darunavir
DDI	Drug-Drug Interaction
DIBD	Developmental International Birth Date
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
DTG	Dolutegravir
EACS	European AIDS Clinical Society

ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ELISPOT	Enzyme-Linked ImmunoSpot
ETV	Early Termination Visit
EU	European Union
EudraCT	European Clinical Trials Database
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FTC/F	Emtricitabine
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type-1
IAS	International AIDS Society
IB	Investigator's Brochure
IBI	Invasive Bacterial Infection
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assays
IMP	Investigational Medicinal Product
INI	Integrase Inhibitor
INSTI	Integrase Strand Transfer Inhibitor
IRB	Institutional Review Board
IRIS	Immune Reconstitution Inflammatory Syndrome
ISF	Investigator Site File
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NNRTI	Non-Nucleoside Reverse-Transcriptase Inhibitor
NRTI	Nucleoside Reverse-Transcriptase Inhibitor
OI	Opportunistic Infection
PBMC	Peripheral Blood Mononuclear Cells
PI	Principal Investigator

PI	Protease Inhibitor
QD	quaque die (once daily)
QOL	Quality of Life
QP	Qualified Person
RAL	Raltegravir
RNA	Ribonucleic Acid
RSI	Reference Safety Information
RT	Reverse Transcriptase
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	Tenofovir Alafenamide Fumarate
TDF	Tenofovir Disoproxil Fumarate
TB	Tuberculosis
TFV	Tenofovir
TMG	Trial Management Group
TMF	Trial Master File
US	United States
USM	Urgent Safety Measure

1. BACKGROUND AND RATIONALE

Treatment responses to antiretroviral therapy (ART) have constantly improved. This is due to novel compounds and combinations with improved antiviral efficacy and side effect profiles resulting in less virologic failures and treatment discontinuation. On the other hand, most recent randomised controlled trials for first line treatment consider patients with less advanced disease (mean CD4 cell counts at baseline >350/µl, less than 15% of patients with CD4 cell counts <200/µl) and low baseline viral loads [DeJesus et al., Raffi et al., Walmsley et al., Sax et al, Gallant et al.]. This favours superior overall response rates, as these patients usually suffer from less co-morbidities, drug-drug interactions (DDI), and other risks for treatment failure. The rate of patients with Acquired Immune Deficiency Syndrome (AIDS)-defining events enrolled in these trials was low.

Outside these trials, the number of patients considered as late presenters (CD4 cell count <350/µl) when diagnosed with Human Immunodeficiency Virus (HIV) remains high across Europe [Camoni et al., Montlahuc et al.]. According to a definition proposed in 2009, the term late presentation is used for persons presenting for care with a CD4 count <350 cells/mL or presenting with an AIDS-defining event, regardless of the CD4 cell count. Late presentation with advanced disease is restricted to persons presenting for care with a CD4 count <200 cells/mL or presenting with an AIDS-defining event, regardless of the CD4 cell count [Antinori et al.]. Patients with CD4 cell counts <200/µl and/or AIDS events at first diagnosis are frequent in clinical practice [Rafetti et al, Sobrino-Vegas et al, Late presenters working group in COHERE in EuroCoord et al.].

Strategic trials in this patient group thus far focused on time of treatment initiation to prevent immune reconstitution syndromes (IRIS) [Abdool Karim et al., Blanc et al.] or disease course of already diagnosed opportunistic infections (OIs) [Zolopa et al.; Manzardo C et al.]. The AIDS Clinical Trials Group (ACTG protocol 5164) reported that starting ART within the first 30 days after a diagnosis of non-tuberculosis (TB) OIs was associated with a lower rate of AIDS progression and death, compared to delaying initiation of ART, without an increase in adverse outcomes [Zolopa et al.].

Much less is known about which ART regimens perform best in late presenters in terms of viral efficacy, immune reconstitution, improvement of AIDS-related co-morbidities and adverse events (AEs). No specific combinations have been compared in sufficiently powered randomised clinical trials, and all regimens considered in international guidelines for first line therapies are judged as equal standard of care for these patients. Initially, protease inhibitor (PI) containing regimens were frequently used in patients presenting late or with AIDS defining events [Mussini et al.].

However, specifically regimens containing integrase inhibitors (INI) are promising candidates for treatment combinations in patients with CD4 cell counts <200/µl due to their antiviral activity and rapid decline of viral load, beneficial side-effect profile and metabolism pathways compared to other regimens. Also, integrase inhibitors such as dolutegravir (DTG) and bictegravir (BIC/B) have high genetic barriers, thereby preventing resistance mutation development and ensuring sufficient antiviral activity in case of preexisting mutations against nucleosides [Demarest et al.]. Therefore, in cases when needs ART to be initiated before genotypic testing results are available, current European AIDS Clinical Society (EACS) Guidelines (EACS Treatment Guidelines 9.0) recommend to include a drug with a high genetic barrier to resistance in the first-line regimen (e.g. PI or DTG). Whilst some reports describe a higher risk for IRIS in patients receiving integrase inhibitors [Wijting et al., Dutertre et al., Psichogiou et al.], a meta-analysis did not [Hill et al.]. We therefore propose a strategic clinical trial to compare an INI containing regimen versus a boosted PI regimen in patients with advanced HIV-infection.

1.1 Funding and Collaborators

Gilead Sciences, Inc. (Gilead) is the Funder for this Investigator-led study and will provide financial support, as well as supplying the study drug (Biktarvy®) for the INI containing treatment regimen.

Janssen Pharmaceutica NV (Janssen) will also be providing support for the study by supplying the study drug (Symtuza®) for the boosted PI treatment regimen, as well as funds for the associated study drug management costs.

1.2 Assessment and management of risk

1.2.1 B/F/TAF

Experience from Clinical Studies in Treatment-Naïve Patients

Assessment of adverse reactions (ARs) is based on pooled data from two 48-week controlled clinical studies (GS-US-380-1489 ("Study 1489") and GS-US-380-1490 ("Study 1490")) in which 1274 treatment-naïve patients received B/F/TAF (N=634), abacavir (ABC)/DTG/lamivudine (3TC) (N=315), or DTG+FTC/TAF (N=325).

The ARs are listed below by system organ class and frequency. Frequencies (based on all treatment-emergent AEs, regardless of relationship to study drug) are defined as follows: very common (≥10%), common (≥1% and <10%) or uncommon (≥0.1% and <1%).

NERVOUS SYSTEM DISORDERS

Very common: headache

GASTROINTESTINAL SYSTEM DISORDERS

Very common: diarrhoea

Common: nausea, vomiting, abdominal pain, dyspepsia, flatulence

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Common: rash

GENERAL DISORDERS AND ADMINISTRATION SITE REACTIONS

Common: fatigue

Changes in Serum Creatinine: BIC has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 48. In Studies 1489 and 1490, median (Q1, Q3) serum creatinine increased by 0.10 (0.03, 0.17) mg/dL, 0.11 (0.03, 0.18) mg/dL, and 0.11 (0.04, 0.19) mg/dL from baseline to Week 48 in the B/F/TAF, ABC/DTG/3TC, and DTG+FTC/TAF groups, respectively. There were no discontinuations due to renal adverse events through Week 48 in B/F/TAF clinical studies.

Changes in Bilirubin: Total bilirubin increases were observed in 12% of patients administered B/F/TAF through Week 48. Increases were primarily Grade 1 (9%) and Grade 2 (3%) and were not associated with hepatic ARs or other liver related laboratory abnormalities. There were no discontinuations due to hepatic AEs through Week 48 in B/F/TAF clinical studies.

Clinical Experience

The efficacy and safety of B/F/TAF in HIV-1 infected, treatment-naïve adults are based on 48-week data from two randomised, double-blind, active-controlled studies, Study 1489 (N=629) and Study 1490 (N=645).

The efficacy and safety of B/F/TAF in virologically-suppressed HIV-1 infected adults are based on 48-week data from a randomised, double-blind, active-controlled study, GS-US-380-1844 ("Study 1844")

(N=563); and a randomised, open-label, active-controlled study, GS-US-380-1878 ("Study 1878") (N=577).

The efficacy and safety of FTC+TAF (components of B/F/TAF) in HIV-1 infected, virologically-suppressed patients with mild to moderate renal impairment is based on 144-week data from an open-label study, GS-US-292-0112 ("Study 112") (N=242).

The efficacy and safety of FTC+TAF in adult patients coinfected with HIV-1 and chronic hepatitis B (HBV) are based on 48-week data from an open-label study, GS-US-292-1249 ("Study 1249") (N=72). The efficacy and safety of B/F/TAF in adult patients coinfected with HIV-1 and chronic HBV are also supported by 48-week data in 8 HIV/HBV coinfected adults treated with B/F/TAF in Study 1490 and 8 HIV/HBV coinfected adults treated with B/F/TAF in Study 1878.

Treatment-Naïve Patients

In Study 1489, patients were randomised in a 1:1 ratio to receive either B/F/TAF (N=314) or ABC/DTG/3TC (600/50/300 mg) (n=315) once daily. In Study 1490, patients were randomised in a 1:1 ratio to receive either B/F/TAF (N=320) or DTG+FTC/TAF (50+200/25 mg) (N=325) once daily.

In Studies 1489 and 1490, the mean age was 35 years (range 18-77), 89% were male, 58% were White, 33% were Black, and 3% were Asian. 24% of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 1.3-6.6). The mean baseline CD4+ cell count was 460 cells/mm^3 (range 0-1636) and 11% had CD4+ cell counts less than 200 cells/mm^3. 18% of patients had baseline viral loads greater than 100,000 copies/mL. In both studies, patients were stratified by baseline HIV-1 RNA (≤100,000 copies/mL, >100,000 copies/mL to ≤400,000 copies/mL, or >400,000 copies/mL), by CD4 count (<50 cells/µL, 50-199 cells/µL, or ≥200 cells/µL), and by region (US or ex-US).

Treatment outcomes of Studies 1489 and 1490 through Week 48 are presented in Table 1-1.

Table 1-1 Pooled Virologic Outcomes of Studies 1489 and 1490 at Week 48 in Treatment-Naïve Patients[a]

	B/F/TAF (N=634)[b]		**ABC/DTG/3TC (N=315)[c]**	**DTG+FTC/TAF (N=325)[d]**
HIV-1 RNA < 50 copies/mL	91%	93%	93%	
Treatment Difference (95% CI) B/F/TAF vs Comparator	-	-2.1% (-5.9% to 1.6%)	-1.9% (-5.6% to 1.8%)	
HIV-1 RNA ≥ 50 copies/mL[e]	3%	3%	1%	
No Virologic Data at Week 48 Window	6%	4%	6%	
Discontinued Study Drug Due to AE or Death[f]	<1%	1%	1%	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[g]	4%	3%	4%	
Missing Data During Window but on Study Drug	2%	<1%	1%	

[a] Week 48 window was between Day 295 and 378 (inclusive).
[b] Pooled from Study 1489 (N=314) and Study 1490 (N=320).
[c] Study 1489
[d] Study 1490
[e] Includes patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an AE, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
[f] Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[g] Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

B/F/TAF was non-inferior in achieving HIV-1 RNA < 50 copies/mL at Week 48 when compared to ABC/DTG/3TC and DTG+FTC/TAF, respectively. Treatment outcomes were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.

In Studies 1489 and 1490, the mean increase from baseline in CD4+ count at Week 48 was 207, 229, and 201 cells/mm^3 in the pooled B/F/TAF, ABC/DTG/3TC, and DTG+FTC/TAF groups, respectively.

Bone Mineral Density: In Study 1489, bone mineral density (BMD) change from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry. In patients who had both baseline and Week 48 hip and lumbar spine BMD measurements (N=257 and 267 in the B/F/TAF group and N=270 and 274 in the ABC/DTG/3TC group, for hip and lumbar spine, respectively), mean percentage changes in BMD were similar in the B/F/TAF group compared to the ABC/DTG/3TC group for hip (-0.8% vs -1.0%) and lumbar spine (-0.8% vs -0.6%).

Pharmacology

Mechanism of Action:

BIC: BIC is an Integrase Strand Transfer Inhibitor (INSTI) that binds to the integrase active site and blocks the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

BIC has activity that is specific to HIV-1 and HIV-2.

FTC: FTC is a nucleoside analogue of 2'-deoxycytidine. FTC is phosphorylated by cellular enzymes to form FTC triphosphate. FTC triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase (RT), which results in DNA chain-termination.

FTC has activity that is specific to HIV-1 and HIV-2 and HBV.

FTC triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria in vitro and in vivo.

TAF: TAF is a phosphonamidate prodrug of TFV (2'-deoxyadenosine monophosphate analogue). TAF is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than TDF in loading TFV into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite TFV diphosphate. TFV diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination.

TFV has activity that is specific to HIV-1 and HIV-2 and HBV. In vitro studies have shown that both FTC and TFV can be fully phosphorylated when combined in cells. TFV diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity in vitro based on several assays including mitochondrial DNA analyses.

Antiviral Activity:

B/F/TAF: The triple combination of B, F and TAF demonstrated synergistic antiviral activity in cell culture.

BIC: The antiviral activity of BIC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4+ T-lymphocytes. The EC_{50} values for BIC were in the range of < 0.05 to 6.6 nM. The protein-adjusted EC_{95} of BIC was 361 nM for wild type HIV-1 virus.

BIC displayed antiviral activity in cell culture against HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from < 0.05 and 1.71 nM), and activity against HIV-2 (EC_{50} = 1.1 nM).

In a study of BIC with representatives from the major classes of approved anti-HIV agents (nucleoside reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), INSTIs, and PIs), additive to synergistic antiviral effects were observed. No antagonism was observed for these combinations.

FTC: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI CCR5 cell line, and PBMCs. The EC_{50} values for FTC were in the range of 0.0013 to 0.64 µM.

FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 µM) and showed activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 µM).

In two-drug combination studies of FTC with NRTIs, NNRTIs, PIs, and INSTIs, additive to synergistic effects were observed. No antagonism was observed for these combinations.

TAF: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4 T lymphocytes. The EC_{50} values for TAF were in the range of 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 and 12.0 nM), and activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs), additive to synergistic antiviral effects were observed. No antagonism was observed for these combinations.

<u>Pharmacokinetic Properties</u>

Absorption:

BIC: BIC is absorbed following oral administration with peak plasma concentrations occurring at 2-4 hours after administration of B/F/TAF. Relative to fasting conditions, the administration of B/F/TAF with either a moderate fat (~600kcal, 27% fat) or high fat meal (~800kcal, 50% fat) resulted in an increase in BIC AUC (24%). This modest change is not considered clinically meaningful and B/F/TAF can be administered with or without food.

FTC: FTC is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1.5-2 hours after administration of B/F/TAF.

The mean absolute bioavailability of an FTC 200 mg capsule was 93%. The mean absolute bioavailability of the FTC 10 mg/mL oral solution was 75%.

FTC systemic exposure was unaffected when FTC was administered with food and B/F/TAF can be administered with or without food.

TAF: TAF is rapidly absorbed following oral administration with peak plasma concentrations occurring at 0.5-2 hours after administration of B/F/TAF.

Relative to fasting conditions, the administration of TAF with a moderate fat meal (~600kcal, 27% fat) and a high fat meal (~800kcal, 50% fat) resulted in an increase in AUC_{last} of 48% and 63% respectively. These modest changes are not considered clinically meaningful and B/F/TAF can be administered with or without food.

B/F/TAF: The multiple dose PK parameters of the components of B/F/TAF are provided in Table 1-2.

Table 1-2 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of B/F/TAF With or Without Food in HIV-Infected Adults.

Parameter Mean (%CV)	Bictegravir[a]	Emtricitabine[b]	Tenofovir Alafenamide[c]
C_{max} (microgram per mL)	6.15 (22.9)	2.13 (34.7)	0.121 (15.4)
AUC_{tau} (microgram·hour per mL)	102 (26.9)	12.3 (29.2)	0.142 (17.3)
C_{trough} (microgram per mL)	2.61 (35.2)	0.096 (37.4)	NA

CV = Coefficient of Variation; NA = Not Applicable

[a] From Population PK analysis in Studies 1489, 1490, 1844, and 1878; N = 1193

[b] From Intensive PK analysis in Studies 1489, 1490, 1844, and 1878; N = 77

[c] From Population PK analysis in Studies 1489 and 1490; N = 486

Please refer to the Biktarvy® Summary of Product Characteristics (SmPC) for further information about clinical studies involving BIC.

1.2.2 Risk/Benefit Assessment for the Study

All patients with HIV-1 infection should receive effective ART. Potential risks associated with all classes of ARVs include IRIS. The risk of class effects is considered to be low. Important identified risks appropriately managed by study inclusion/exclusion criteria as well as through close clinical and laboratory monitoring during the study, are as follows: hypersensitivity reaction, including liver injury, and allergy to any components of the regimens. Interim data will also be reviewed by an independent data monitoring committee.

Potential benefits may include provision of a new ART that is not currently available, and which may have fewer side effects than alternative therapies. The benefits of participation for patients receiving B/F/TAF include provision of a therapy with less DDI due to the non-boosting regimen. Other potential benefits include provisions of fixed dose combination (FDC) therapy, and the knowledge that patient participation will contribute to the body of knowledge of HIV therapies.

Following a chronic 39-week study in monkeys, animals administered the highest dose of BIC (1000 mg/kg/day) had bile duct hyperplasia (increased cell growth) and hypertrophy (increased cell size), and some increased cell growth and inflammation in nearby liver cells. These effects were not seen in monkeys administered the mid-level dose (200 mg/kg/day), and these animals had plasma BIC exposures that were approximately 5-fold above human exposures when given the B/F/TAF FDC. No adverse drug reactions associated with liver or bile duct problems have been identified in humans treated with BIC.

Darunavir as a component of D/C/F/TAF fix-dose combination can cause transient and usually asymptomatic elevations in serum aminotransferase levels and has been linked to rare instances of clinically apparent, acute liver injury. No dose adjustment of D/C/F/TAF is required in patients with mild or moderate (Child-Pugh Class A/B) hepatic impairment or in patients with estimated glomerular filtration rate according to the Cockcroft-Gault formula (eGFRCG) ≥ 30 mL/min. The most frequent adverse reactions reported were diarrhea, nausea, fatigue, headache, and rash. Darunavir contains a sulphonamide moiety and should be used with caution in patients with a known sulphonamide allergy. Co-administration of D/C/F/TAF and medicinal products primarily metabolised by CYP3A may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions.

The overall benefit-risk assessment for B/F/TAF and D/C/F/TAF is favourable at this time.

1.2.3 Rationale for Dose Selection

B/F/TAF

The B/F/TAF FDC containing B (50 mg), F (200 mg), and TAF (25 mg), has been approved by the Food and Drugs Administration (FDA) for use once daily for the treatment of HIV-1 infection in adults. This regimen has been submitted to the European Medicines Agency for approval and was approved in June 2018. Phase 3 clinical trials with the B/F/TAF FDC in treatment-naïve patients have shown it to be safe and well tolerated and have demonstrated non-inferiority to ABC/DTG/3TC and DTG + F/TAF at Week 48 by snapshot algorithm (GS-US-380-1489 and GS-US-380-1490). B/F/TAF contains 25 mg of TAF, the approved and recommended dosage for the treatment of HBV infection with other antiretrovirals (ARVs) for treatment of HIV/HBV co-infection (Please refer to the Biktarvy® SmPC for further information).

D/C/F/TAF

The D/C/F/TAF FDC (Symtuza®) containing D (800 mg), C (150 mg), F (200 mg), and TAF (10 mg), has been approved in the European Union (EU) for use once daily for the treatment of HIV-1 infection in adults.

2. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

2.1 Primary objective

- To demonstrate the non-inferiority of an INI containing regimen [bictegravir (B)/emtricitabine (F)/tenofovir alafenamide (TAF) QD] versus a boosted PI regimen [darunavir (D)/cobicistat (C)/ emtricitabine (F)/tenofovir alafenamide (TAF) QD] in patients with advanced HIV infection.

2.2 Secondary objectives

- To investigate the immunological and virological response, tolerability, resistance development, discontinuation of therapy due to tolerability, quality of life (QoL) and IRIS incidence.

2.3 Exploratory objectives

- To assess whether virological response is better predicted by deep sequencing rather than standard population sequencing.

2.4 Outcome measures/endpoints

2.4.1 Primary endpoint/outcome

- Time to failure, as the first occurrence of any of the following components:

1. Virological reasons
   a) Insufficient virological response, either:
      a. HIV-1 RNA reduction < 1 log 10 copies/mL at week 12, or
      b. Viral load > 50 HIV-1 RNA copies/mL at week 48

b) Viral rebound, which is subsequently confirmed at the following scheduled or unscheduled visit, defined as either:
    a. Rebound of HIV-1 RNA to >200 copies/mL after having achieved HIV-1 RNA <50 copies/mL
    b. Rebound of HIV RNA by >1 log 10 copies/mL from nadir value, for patients whose viral load has never been suppressed below 50 copies/mL

2. Clinical reasons*
    a) Death related to HIV, AIDS, OI/severe BI or complications of therapy including IRIS
    b) Any new or recurrent AIDS defining event on, or after 28 days of therapy
    c) Any new serious non-AIDS defining event documented by the endpoint review committee (including severe BI, end stage liver disease, renal failure, cardiovascular event, and non-AIDS related malignant disease)
    d) Clinically relevant AEs of any grade or IRIS which require treatment interruption (lasting > 5 days) of INI or boosted PI therapy within the first 48 weeks after randomisation
    Note: Discontinuation of BIC or boosted DRV followed by (within 5 days) continuation with another INI or PI, respectively, is not considered as a strategy failure or endpoint.

2.4.2 Secondary endpoints/outcomes

- Proportion of patients with HIV-RNA viral load < 50 copies/mL at week 24, 36, 48
- HIV-1 drug resistance at confirmed virological failure (genotype)
- Time to reach CD4 count > 200/µL (first measurement)
- Proportion of patients with CD4 cell count < 200 µL and < 350µL at week 4, 8, 12, 24, 36, 48
- CD4/CD8 ratio at week 4, 8, 12, 24, 36, 48
- Incidence of IRIS in the two arms through week 48
- Incidence and duration of hospitalisation, rate of relapse of specific OI/BI through week 48
- Safety and tolerability, measured by Grade 2, 3 and 4 signs and symptoms and laboratory toxicities through week 48
- ART and OI/BI treatment changes and dose modifications due to toxicities and DDI with ART, and IRIS through week 48
- Health care resource use, including total inpatient days and emergency room visits through week 48
- QOL and functional status outcomes, including overall self-reported QOL and functional status compared in the two groups at week 48
- Discontinuation or modification of study medication due to insufficient virological response, resistance mutations at baseline, or resistance mutation development before week 48

2.4.3 Exploratory endpoints/outcomes

- Mutations detected by deep sequencing compared with those detected by population sequencing
- Proportion of patients with HIV-RNA viral load < 50 copies/mL at week 4, 8, 12

* Refer to Appendices 3 (AIDS-Defining Conditions), 4 (INSIGHT Serious Non-AIDS Events Criteria), 5 (INSIGHT Progression of HIV Disease Criteria) and 6 (Immune Reconstitution Inflammatory Syndrome Generic Criteria).

3 TRIAL DESIGN

An open-label, randomised, two arm, multicentre trial over 48 weeks to compare two strategies for HIV-1 infected patients with advanced disease, stratified according to country and baseline CD4 cell count (<50 cells/µL, 50-199 cells/µL, or ≥200 cells/µL).

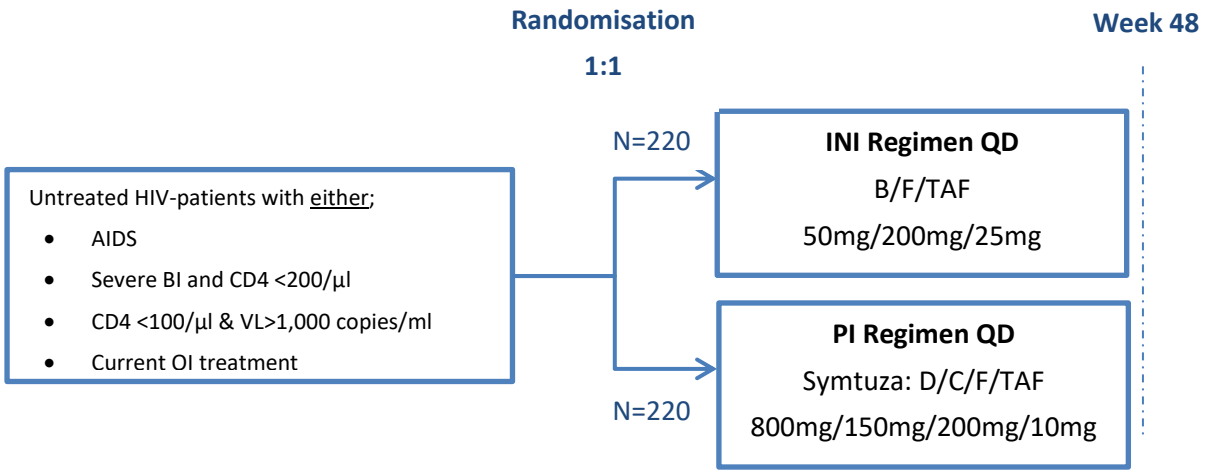
Patients will be randomised to receive either an integrated inhibitor containing regimen (B (50mg)/F (200mg)/TAF (25mg) [1 pill administered orally once daily for 48 weeks]) or a boosted PI regimen (D (800mg)/C (150mg)/F(200mg)/TAF (10mg) [1 pill administered orally once daily for 48 weeks]).

Study visits will take place at screening, baseline, weeks 4, 8, 12, 24, 36 and 48, as well as a follow-up visit 30 days following the week 48 visit.

Routine investigations will include HIV-1 RNA, CD4, CD8, haematology (including haemoglobin, white cell count and differential, platelets), biochemistry (including sodium, potassium, creatinine, phosphorus, albumin, glucose, alanine transaminase (ALT), aspartate aminotransferase (AST), ALP, total and indirect bilirubin, total cholesterol, HDL, LDL, triglycerides), QoL questionnaire (EuroQoL EQ-5D-3L), HIV Symptom Index (HIV-SI/SDM) urine sample (for haematuria, proteinuria, glycosuria, leukocytes, nitrites, pregnancy test in women of child-bearing potential (WOCBP)).

For a full list of investigations please see the table of assessments in Appendix 1.

3.1 Study Schema



4 STUDY SETTING

This study will be conducted within the NEAT ID network and include sites that have an excellent track record in clinical research and operate in up to eight countries. A full feasibility and qualification assessment plan will be undertaken for all potential sites. The sponsor will ensure that onsite visits are performed to assess GCP compliance, including (but not limited to); protocol adherence, informed consent documentation, data quality, drug accountability and overall site performance.

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for participation into this study.

1. The ability to understand and sign a written informed consent form (ICF) and must be willing to comply with all study requirements.

2. Male or non-pregnant, non-lactating females.

3. Age ≥ 18 years.

4. Has documented, untreated HIV-1 infection with either:

   a) AIDS with any CD4 cell count (AIDS-defining conditions are listed within Appendix 3).

   Or

   b) Severe bacterial infection (BI)[†] and must have a CD4 cell count < 200/µl within 30 days prior to study entry.

   Or

   c) Are asymptomatic with CD4 cell count < 100/µL within 30 days prior to study entry and must have an entry HIV viral load > 1000 copies/mL.

   Or

   d) Currently receiving treatment for OI[‡].
      i. Subjects with other serious OIs, including other AIDS-defining and AIDS-related OIs for which appropriate therapy other than ART exists are eligible, but Investigator approval must be obtained.
      ii. Current OI treatment must have been started ≤ 14 days prior to study entry but can have been discontinued prior to study entry.

5. Have the ability to take oral medications.

6. Females of childbearing potential and heterosexually active males must be willing to use a highly effective method of contraception and be willing to continue practising these birth control methods during the trial and for at least 30 days after the last dose of study medication. See Appendix 7 for further details.

[†] A severe BI consists of any of bacterial pneumonia, IBI or any bacterial infectious disorder with grade 3 severity or requiring unscheduled hospital admission. An IBI is defined as the isolation of a bacterial organism from a normally sterile body site, or for bacterial nucleic acid to be detected at a normally sterile body site. Sterile body sites include blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, joint fluid, bone aspirate, or a deep tissue abscess.

[‡] Including Pneumocystis jrovecii pneumonia [PCP]; disseminated histoplasmosis; cytomegalovirus [CMV] infection; toxoplasmic encephalitis; other atypical non-tuberculous, non-MAC mycobacterial infections; or other serious, invasive bacterial infections (IBI).

Such methods include:

- True abstinence from penile-vaginal intercourse, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception).
- Non-hormonal Intrauterine device or non-hormonal intrauterine system that meets the effectiveness criteria as stated in the product label.
- Male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject.
- Combined (oestrogen and progesterone containing) hormonal contraception associated with the inhibition of ovulation*:
  - Oral
  - Intravaginal
  - Transdermal
- Bilateral tubal occlusion

- Note: Non-childbearing potential is defined as either post-menopausal (had amenorrhea for at least 12 months and have an FSH (follicle stimulating hormone) of greater than 40 IU/L or, if FSH testing is not available, they have had amenorrhea for 24 consecutive months) or physically incapable of becoming pregnant with documented hysterectomy , bilateral salpingectomy or bilateral oophorectomy).

*If a patient is randomised to Symtuza, an alternative highly effective method of contraception should be used

5.2 Exclusion criteria

1. Any ARV prior to study entry.

2. Systemic cancer chemotherapy within 30 days prior to study entry, or current treatment for cancer (with the exception of Kaposi's sarcoma) or lymphoma.

3. Current or anticipated use of contraindicated medications (see Summary of Product Characteristics (SmPC) for Symtuza® and Biktarvy®) or anticipated systemic chemotherapy during study enrolment (administration of any contraindicated medication must be discontinued at least 30 days prior to the baseline visit and for the duration of the study).

4. Known resistance to the components of study medications (see section 6.1.3 for more details).

5. History or symptoms of advanced renal and/or hepatic impairment. Such as, kidney failure requiring dialysis; eGFR <30 mL/min; hepatic transaminases (AST and ALT) > 5 x upper limit of normal (ULN); or, platelet count <50,000.

6. Current drug or alcohol use that, in the opinion of the Investigator, would cause interference with the study.

7. Cryptococcal meningitis or active TB or current or expected treatment requiring Rifampicin or Rifabutin (patients with expected latent TB will have a TB test (IGRAs e.g. ELISPOT, QuantiFERON etc.) at their screening visit).

8. History or presence of allergy to the study drugs or their components, or drugs of their class.
9. Using any concomitant therapy disallowed as per the product labelling for the study drugs.
10. Any investigational drug within 30 days prior to the study drug administration.
11. Patients with severe (Child Pugh class C) hepatic impairment.
12. Women who are pregnant, breastfeeding or plan to become pregnant or breastfeed during the study.

6 TRIAL PROCEDURES

The schedule of assessments is summarised in Appendix 1.

Please note that if additional tests/procedures are required in accordance with local practice, then these should still be performed (no usual tests/procedures should be withheld from the patients during the study).

6.1 Recruitment

Following full written informed consent, sites must keep a record of all screening and enrolled participants using screening and enrolment logs. Diagnostic tests procedures may be used in determining eligibility however, written informed consent must be obtained prior to any study specific procedures. All information collected for eligible participants will be pseudo-anonymised and recorded in the Investigator Site File (ISF).

All eligible consented participants will be given a unique study identifier via an electronic study database.

Anonymised information that will be collected:

- age
- gender
- ethnicity
- whether the patient is enrolled or not enrolled
- if the patient is deemed ineligible, then the reason for this; or if they are eligible but choose not to participate, then their reason for declining (where available)

6.1.1 Patient identification

Patients will be identified through clinic visits by their direct study medical care team and visits will be captured on a participant screening log. Additionally, Investigators may use advertisements; however, these must be approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB) prior to use.

6.1.2 Screening

Written informed consent must be obtained from the subject prior to performing any study related evaluations or procedures.

Subjects will be provided with written information about the study in the form of a subject information sheet and will be allowed adequate time for questions and to consider the study before agreeing to participate. It will be the responsibility of the Investigator or co-investigator to obtain written informed consent prior to undertaking any procedures detailed in the protocol. This responsibility may be delegated to other suitably trained personnel if allowed according to country-specific regulations and approved by the local IEC.

The Investigator or designee must provide adequate explanation of the aims, methods, objectives and potential hazards of the study. It must also be explained to the subject that they are free to refuse or withdraw from the study for any reason without detriment to their future care or treatment.

See Appendix 1 for details of screening assessments required.

6.1.3 Resistance Testing and Results

Resistance test results obtained at screening may influence randomisation.

If resistance data of the RT, protease (Table 1 and 2), or integrase gene as described below become available after screening but before randomisation patients should not be randomised (and will be seen to be screen failures).

If data becomes available after randomisation, patients may be considered to switch to the other treatment arm at the investigator's discretion in the following scenarios:

1. Patients randomised to the DRV arm may be considered to switch to the BIC arm only if they have any of the resistance mutation patterns as described in Table 1. In these patients, only TAF and FTC would have full ARV activity. The decision should be made by the investigator after consultations with the LAPTOP study team.

Table 1: Resistance mutation patterns leading to intermediate of high-level resistance against DRV.

Resistance	**Mutation pattern[21]**											
Darunavir	V32I	L33F	K43T	M46I	I47V	I54L/M	G73T/S	L76V	V82A	I84V	L89V	L90M
Intermediate						L						+
Intermediate		+				L	T			+		+
Intermediate				+				+		+		
High	+		+	+	+	M			+			+
High	+	+		+	+	M			+			+
High	+					M	S			+	+	+

2. Patients randomised to the DRV or BIC arm may be considered to remain in their treatment arm or to switch to an alternative regime (e.g. PI + INI) only if they have any of the resistance mutation pattern as described in Table 2. Table 2 describes RT inhibitor associated resistance mutation pattern, in which intermediate or high-level resistance against FTC and TFV has to be expected. In these situations, only DRV or BIC would have full ARV activity. The decision to remain on therapy or to switch should be made by the investigator after consultations with the LAPTOP study team.

Table 2: Resistance mutation patterns leading to intermediate of high-level resistance against FTC or tenofovir disoproxil fumarate (TDF).

Resistance		**Mutation pattern**									
FTC	***TDF***	M41L	E44D	K65R	D67N	T69D	K70R	M184V/I	L210W	T215Y	K219N/Q
High	Interm	+						V	+	+	
High	Interm				+		+	V		+	Q

High	Interm	+			+			V	+	+	
High	Interm			+				V			
High	Interm			+				I			
High	High	+	+		+				+	+	
High	High	+	+		+	+		V	+	+	
High	High	+	+		+			V	+	+	N

If any primary integrase strand transfer inhibitor resistance mutation (T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K) is identified please consult the LAPTOP study team. Resistance mutation patterns leading to possible resistance against BIC are Q148H/R/K plus 2 or more of the following mutations: (G140A/C/S, T97A, L74M, or E138A/K).

6.1.4 Consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to perform their role according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are outside standard routine care at the participating site. The right of a participant to refuse participation without giving reasons must be respected.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

6.1.5 The randomisation scheme

Patients will be randomly allocated (1:1) to receive a BIC containing regimen or boosted PI containing regimen for 48 weeks. Randomisation will be computer-generated in permuted blocks and stratified by country and baseline CD4 cell count (<50 cells/µL, 50-199 cells/µL, or ≥200 cells/µL). Randomisation will be done at the baseline visit (date of the study treatment initiation). This study is open-label, therefore, all investigators, site pharmacists, study nurses and subjects will be unmasked and aware of the treatment allocation throughout the study.

6.1.6 Method of implementing the allocation sequence

The method will be detailed in the randomisation plan.

6.2 Baseline data

See Appendix 1 for details of assessments required.

6.3 Treatment Phase Assessments

See Appendix 1 for details of assessments required.

6.4 Follow-Up/Early Termination Visit (ETV)

In the case of early termination, every attempt will be made to ensure the subject has a termination visit. Patients will be encouraged to attend for remaining visits and complete study assessments to week 48 even if they are no longer taking study medication.

See Appendix 1 for details of assessments required.

6.5 Withdrawal criteria

A subject is free to withdraw from the study at any time. In addition, the Investigator may decide, for reasons of medical prudence, to stop study medication (e.g. lack of efficacy).

All patients who discontinue study medication will be followed up and encouraged to attend for study visits up until week 48.

If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study and the reason for withdrawal recorded in the Case Report Form (CRF).

Study medication may also be discontinued in the following instances:

1. If the subject withdraws their consent.
2. If the investigator considers in the interest of the subject (i.e. intercurrent illness, unacceptable toxicity) that it is best for them to stop study medication.
3. The subject fails to comply with the protocol requirements or fails to cooperate with investigator.
4. Pregnancy during the study (for patients receiving B/F/TAF, the study medication must be discontinued).
5. Discontinuation of the study at the request of the Sponsor, regulatory agency, or an IRB/IEC.

The date and reasons for stopping medication will be clearly stated on the subject's CRF and source document. Every attempt should be made to arrange follow up visits for subjects who are withdrawn from study medication. This visit should involve assessments as outlined in Appendix 1.

Subjects withdrawing from the trial should be offered alternative treatment as per the local standard of care by the Investigator.

Additional subjects may be recruited to account for any withdrawals should this be deemed necessary by the statistician or CI.

6.6 Storage and analysis of samples

All samples (with the exception of centrally analysed resistance samples) will be analysed at each site's local laboratory. After analysis the samples will be destroyed in accordance with local laboratory requirements. Throughout the study a total of 234ml of blood will be collected from each patient, this equates to 26ml per visit.

Collection, processing and storage instructions will be detailed in a separate laboratory manual.

6.6.1 Resistance testing

Next generation sequencing (deep sequencing) may be performed centrally to evaluate the significance of the HIV-1 mutations detected by this method, which are identified during standard population sequencing of the HIV viral load response.

Blood samples for these tests will be taken at the baseline visit and treatment phase visits (Week 4, 8, 12, 24, 36 and 48). A sample will be taken at the ETV for patients with virological failure identified outside of a scheduled visit.

Samples will be shipped on a periodic basis from the sites to ACM Global for central storage and shipped to Monogram Biosciences for analysis.

At the end of the study, samples taken from patients that do not have virological failure will be destroyed, either locally, or at ACM Global.

Collection, processing and storage instructions will be detailed in a separate laboratory manual.

See Appendix 1 for details of assessments required.

6.7 Virological Failure

Virological failure is defined as:

Insufficient virological response, either:

- HIV-1 RNA reduction < 1 log 10 copies/mL at week 12, or
- Viral load > 50 HIV-1 RNA copies/mL at week 48

Or viral rebound, which is subsequently confirmed at the following scheduled or unscheduled visit, defined as either:

- Rebound of HIV-1 RNA to >200 copies/mL after having achieved HIV-1 RNA <50 copies/mL
- Rebound of HIV RNA by >1 log 10 copies/mL from nadir value, for patients whose viral load has never been suppressed below 50 copies/mL

Local resistance testing should also be carried out in the event of viral failure from the first sample and patients should discontinue study medication and receive rescue medication at investigators discretion.

6.8 End of trial

The end of the trial is defined as the date of the last visit of the last subject undergoing the trial in any country.

The sponsor must notify the Competent Authority (CA) and main IRB/IEC of the end of a clinical trial within 90 days of its completion.

7 TRIAL MEDICATION

Name and description of investigational medicinal product(s)

At baseline, participants will be enrolled into one of two treatment arms, either a BIC-based regimen or a DRV-based regimen:

INI containing regimen (BIC-based regimen): One combined B 50mg/F 200mg/TAF 25mg tablet taken orally once daily for up to 48 weeks without regard to food.

Boosted PI regimen (DRV-based regimen): One combined D 800mg/C 150mg/F 200mg/TAF 10mg tablet taken orally once daily for up to 48 weeks with the addition of food.

Participants will take the study medication from baseline, as randomised, to week 48.

Please refer to the study specific pharmacy manual for more information.

7.1 Summary of Product Characteristics (SmPC), Investigator's Brochure (IB) and Reference Safety Information (RSI)

Information about Emtricitabine (Emtriva®, F/FTC)

Emtricitabine (5-fluoro-1-[(2R, 5S)-2-(hydroxymethyl)-[1, 3]-oxathiolan-5-yl] cytosine, FTC) is a NRTI that has demonstrated potent and selective inhibition of the HIV. In HIV-infected adults, FTC is administered as a 200mg QD dose concurrently with other ARV drugs. The 200mg FTC capsule formulation was approved by the United States (US) FDA for marketing on 2 July 2003 and is available under the name Emtriva®. In the European Union (EU), marketing authorisation was granted for both the 200mg Emtriva® capsule formulation and a 10mg/mL Emtriva® oral solution formulation on 24 October 2003, with indications for the treatment of HIV infection concurrently with other ARV drugs in both adult and pediatric patients.

Further information is available in the current Prescribing Information for Emtriva®.

Information about Tenofovir alafenamide (TAF, GS-7340)

Tenofovir alafenamide (GS-7340, TAF) is a second-generation oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. TFV is metabolised intracellularly to the active metabolite, tenofovir diphosphate, a competitive inhibitor of HIV-1 RT that terminates the elongation of the viral DNA chain. The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV.

Further information about the co-formulated version of TAF/FTC is available in the current Prescribing Information for Descovy®.

Information about Darunavir (Prezista ®, D/DRV)

Prezista® is a PI which demonstrated potent inhibition of the HIV. DRV received marketing authorisation valid throughout the EU 12/02/2007. Co-administered with low dose ritonavir is indicated in combination with other ARV medicinal products for the treatment of HIV-1 infection in adult and paediatric patients from the age of 3 years and at least 15 kg body weight. Co-administered with cobicistat (C) is indicated in combination with other ARV medicinal products for the treatment of HIV-1 infection in adult patients. In ART-naïve adult patients the recommended dose regimen is 800 mg once daily with C 150 mg once daily or ritonavir 100 mg once daily taken with food.

Further information about DRV is available in the current Prescribing Information for Prezista®.

Information about Darunavir/Cobicistat/Emtricitabine/Tenofovir alafenamide (D/C/F/TAF) fixed dose combination (Symtuza®)

Symtuza® is a boosted PI indicated for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg). Symtuza® received marketing authorisation valid throughout the EU in September 2017. The recommended dose regimen in adults and adolescents aged 12 years and older, weighing at least 40 kg, is one tablet taken once daily with food. Each film coated tablet contains 800 mg of D (as ethanolate), 150 mg of C, 200 mg of F, and 10 mg of TAF.

Further information about the D/C/F/TAF FDC is available in the current Prescribing Information for Symtuza®.

The Reference Safety Information for this regimen will be the Summary of Product Characteristics for Symtuza®.

Bictegravir (BIC)

BIC is an inhibitor of HIV-1 integrase that is being evaluated for the treatment of HIV-1 infection. Antiviral testing has shown that BIC is active against a broad panel of HIV-1 viral lab strains and clinical isolates. BIC is fully active against a panel of mutant viruses with resistance to NRTIs, NNRTIs, and PIs. Integrase mutant viruses that are resistant to the INSTIs raltegravir (RAL) and elvitegravir (EVG) remain largely sensitive to BIC. Gilead Sciences (Gilead) has co-formulated BIC with the NRTI F and TAF into an FDC tablet that is suitable for once-daily use.

Further information about the B/F/TAF fix-dose tablet is available in the current Prescribing Information for Biktarvy®.

The Reference Safety Information for this regimen will be the Summary of Product Characteristics for Biktarvy®.

7.2 Drug storage and supply

Investigators are to ensure that the investigational medicinal product (IMP) is only used in accordance with the protocol. Drug supplies will be kept in a secure, limited access storage area under the recommended storage conditions, and accessible only to those authorised by the investigator to dispense to eligible subjects.

The investigator will ensure that records are maintained showing the receipt and dispensation for all study supplies. A drug accountability log will be kept with the investigational supplies for reconciliation purposes. This should be used to record the identification of the subject to whom the IMP was dispensed, the date and quantity dispensed, and the quantity unused/returned by the subject. This will be verified by the study monitor.

Partially used or empty containers may be destroyed by the pharmacy/designee at local site only after the study monitor has completed drug accountability. The pharmacy/designee are required to document destruction for verification by the sponsor.

Further information can be found in the pharmacy manual.

7.3 Preparation and labelling of Investigational Medicinal Product

Both the INI containing regimen (B/F/TAF) and the boosted PI regimen (D/C/F/TAF) tablets will be labelled with Annex 13 compliant labels and QP certified by PCI Pharma Services; who will supply directly to each site on request of the sponsor.

Further information can be found in the pharmacy manual.

7.4 Dosage schedules

Patients will be randomised into one of two treatment arms.

INI containing regimen (BIC-based regimen): One combined B 50mg/F 200mg/TAF 25mg tablet taken orally once daily for up to 48 weeks without regard to food.

Boosted PI regimen (DRV-based regimen): One combined D 800mg/C 150mg/F 200mg/TAF 10mg tablet to be taken orally once daily for up to 48 weeks with the addition of food.

7.5 Dosage modifications

Please refer to section 6.5 for withdrawal and stopping rules.

Treatment modification will be captured as a secondary endpoint only and modifications will be based on the treating physician's judgement.

7.6 Known drug reactions and interaction with other therapies

See section 8.2 and RSI.

Drugs that affect the study medication and that are affected by the use of the study medication accordingly must be reviewed by the Investigator and/or avoided.

7.7 Concomitant medication

For a full list of contraindicated medications, please refer to the current SmPC for both Biktarvy® and Symtuza® (details can be found at https://www.medicines.org.uk/emc/).

Prophylaxis for specific OI or TB shall be performed as per standard of care. Reference can be made to the EACS guidelines.

7.8 Trial restrictions

Please refer to inclusion and exclusion criteria listed in sections 5.1 and 5.2.

7.9 Assessment of adherence

Adherence during the trial will be monitored by subject questioning regarding missed tablets at each visit. The outcome of this questioning should be documented in the patient notes. Issues of adherence should be reported to the study monitor.

All subjects should return unused medication and containers at weeks 12, 24, 36 and 48 for pharmacy accountability purposes (see section 7.2).

7.10 Provision of treatment after the end of the trial

No post trial medication will be provided to patients. Following their last treatment visit at Week 48 patients will receive treatment as per local standard of care.

8 PHARMACOVIGILANCE

8.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

	The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as ARs.
Serious Adverse Event (SAE)	An SAE is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An AE that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the SmPC for that product • in the case of any other investigational medicinal product, in the IB relating to the trial in question

"Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

8.2 Operational definitions for (S)AEs

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the study treatments. An AE can therefore be any unfavourable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

AEs observed by the Investigator, or reported by the subject, and any remedial action taken, will be recorded in the subject's CRF and should be verifiable in the subject's notes throughout the study. The nature of each event, time of onset after drug administration, duration and severity will be documented together with the Investigator's opinion of the causal relationship to the investigational product (unrelated, unlikely, possible, probable, and definite).

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed.

Procedures such as surgery should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy noted on the CRF.

Planned procedures such as surgery scheduled prior to the subject's enrolment into the study do not need to be reported as AEs if these are documented as planned at the screening visit.

Clinically significant changes in physical examination and blood safety profiles should also be recorded as AEs.

8.2.1 Assessment of intensity

Severity should be recorded and graded according to the ACTG Grading Scale (Appendix 2).

Note: There is a distinction between the seriousness and the intensity of an AE. Severe is a measure of intensity; thus, a severe reaction is not necessarily an SAE. For example, a headache may be severe in intensity but would not be classified as serious unless it meets one of the seriousness criteria for serious events.

All events deemed to be Grade 4 (potentially life threatening) according to the ACTG grading scale should be routinely reported as an SAE. However, there may be occasions where in the investigator's clinical judgement they do not consider the event to be life threatening therefore they do not consider the event to meet the definition of an SAE. In these cases, the investigator must document clearly in the participants source documentation that the Grade 4 event has been assessed and why in their clinical judgement they do not consider the event to be life threatening.

8.2.2 Assessment of causality

The relationship to study drug of each AE will be assessed by the PI (or a delegated clinician) using the following definitions:

DEFINITE: distinct temporal relationship with drug treatment. Known reaction to agent or chemical group or predicted by known pharmacology. Event cannot be explained by subject's clinical state or other factors.

PROBABLE: reasonable temporal relationship with drug treatment. Likely to be known reaction to agent or chemical group or predicted by known pharmacology. Event cannot easily be explained by subject's clinical state or other factors.

POSSIBLE: reasonable temporal relationship with drug treatment. Event could be explained by subject's clinical state or other factors.

UNLIKELY: poor temporal relationship with drug treatment. Event easily explained by subject's clinical state or other factors.

UNRELATED: the event occurs prior to dosing. Event or intercurrent illness is due wholly to factors other than drug treatment.

8.2.3 Collection and Follow up of Adverse Events

All AEs, however minor, will be documented in the CRF whether or not the Investigator considers the event to be treatment related.

The AE reporting period will be from consent until the subject's final study visit. In addition, any untoward event that may occur subsequent to the reporting period that the Investigator assesses as possibly, probably or definitely related to the study drug medication should also be reported as an AE.

AEs not already reported in the RSI for the study drugs will be considered unexpected.

AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit.

All AEs should be followed up until they are resolved or the subject's participation in the study ends (i.e. until the final CRF is completed for that subject). In addition, all serious and non-serious AEs assessed by the Investigator as possibly related to the investigational medication should continue to be followed up to last subject visit. Such events should be followed until resolution, until no further change can reasonably be expected, or until 30 days following last subject visit.

8.3 Serious Adverse Events (SAEs)

Definition of an SAE can be found in section 8.1.

The SAE should be reported to the sponsor using the study specific SAE form within 24 hours of a member of the study team becoming aware of the event via the fax number provided on the study pharmacovigilance plan.

8.3.1 Recording and Reporting of SAEs and SUSARs

All SAEs/SUSARs occurring from the time of written informed consent until 30 days post cessation of trial treatment must be recorded on the study specific SAE Form and sent to the sponsor within 24 hours of the research staff becoming aware of the event.

For each SAE/SUSAR the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the Investigator
- whether the event would be considered expected or unexpected

Any change of condition or other follow-up information should be sent to the sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and assessed by the CI as unexpected will be classified as SUSARs. The sponsor will inform the CA, the IRB/IEC and the funder as appropriate of SUSARs within the required expedited reporting timescales.

8.4 Responsibilities

8.4.1 **Principal Investigator (PI):**

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness and causality using the RSI approved for the trial.
2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

3. Ensuring that SAEs and SARs (including SUSARs) are followed up with the Sponsor if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

8.4.2 **Chief Investigator (CI) / delegate or independent clinical reviewer:**

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in reviewing seriousness and causality of SAEs reported.
3. Using medical judgement in assignment of expectedness for all SARs reported using the approved RSI for the trial.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment, protocol and as detailed in the Trial Risk Based Monitoring Plan.
5. Ensure immediate review of all SUSARs.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs as needed.
7. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

8.4.3 **Sponsor:**

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Risk Based Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Safety Monitoring Board (DSMB)/Trial Steering Committee (TSC)) according to the Trial Risk Based Monitoring Plan and committee charter documents.
4. Expedited reporting of SUSARs to the CA and IRB/IEC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for (at least annually) and notifying PIs of updates to the RSI for the trial.
7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the CA and IRB/IEC.

8.4.4 Data Safety Monitoring Board (DSMB):

In accordance with the DSMB Charter, periodically reviewing overall blinded safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

8.4.5 Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing unblinded safety data and liaising with the DSMB regarding safety issues.

8.5 Notification of deaths

Any AE, AR or unexpected AR that results in death should be reported as an SAE. See section 8.3 for SAE reporting format and timelines.

Deaths occurring more than 30 days after the final dose, which are considered to be unrelated to the study medication, should not be reported as an SAE.

8.6 Pregnancy reporting

Pregnancy information for all female participants who become pregnant while participating in the study will be collected on the study specific Pregnancy Reporting Form and should be reported to the Sponsor within 24 hours of becoming aware of the pregnancy or the pregnancy outcome. The participant will also be followed up to determine the outcome of the pregnancy, which will also be reported to the sponsor.

In the event of pregnancy, the participant may be withdrawn from the study (see Section 6.5).

Pregnancies in female partners of male participants should be reported as a special reporting situation (see Section 8.10).

8.7 Overdose

All participants should be counselled about the importance of taking the medications as prescribed and they should understand the quantity of medicine they should be taking. Participants must be told to contact their clinic immediately if they take too much medication. If the overdose fits the criteria of an SAE (see Section 8.1) it should be reported appropriately.

8.8 Reporting urgent safety measures

It is the responsibility of the investigator to apply the appropriate level of Urgent Safety Measure (USM) for the safety and protection of each participant in this study in order to prevent harm. USMs may be applied immediately without prior approval from the sponsor, CA or IRB/IEC. However, they must be reported to the sponsor immediately (within 24 hours) who will then inform the CA and IRB/IEC according to local regulation.

8.9 Development Safety Update Reports

The sponsor will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the CA and IRB/IEC.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

8.10 Special Reporting Situations

Special reporting situations should be reported via email to the sponsor within 24 hours of the research staff becoming aware of the event (as for SAEs).

The special situations include:

- Pregnancy exposure (maternal and paternal), breastfeeding and AEs in infants following exposure from breastfeeding
- Overdose (other than as defined in section 8.7), suspected abuse/misuse of the study product, and dependence
- Medication error
- DDI
- Inadvertent or accidental exposure to the study product (including occupational exposure)
- Any failure of expected of pharmacological or medical device action (i.e. lack of effect) of study product
- Unexpected therapeutic or clinical benefit from use of the study product

- Suspected transmission of an infectious agent via the study product
- Expired drug use and falsified medicine
- Off-label use of study product

Product Quality Complaint (PQC): Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study product after it is released for distribution. A complaint is any indication of the failure of the product to meet consumer or user expectations for quality or to meet performance specifications. It may allege an AR, injury, or malfunction associated with the use of the product. It may also involve the design, literature, packaging, advertising, availability, physical appearance, or promotion of a product.

9 STATISTICS AND DATA ANALYSIS

9.1 Sample size calculation

In the ANRS 146 OPTIMAL trial [Levy et al.], of late presenters, the proportion of patients with severe morbidity (new adverse drug event (ADE), other HIV related diseases, serious non-AIDS events, IRIS and death) was estimated at 12.2% per year in the boosted PI arm. The virological failure was estimated at 20% at week 48 in the DRV/r group of the IMEA 040 DATA study (Slama L et al) that recruited a similar population. As a few subjects will meet more than one of these criteria, we assumed a cumulative probability of failure at 25% at 48 weeks in the PI regimen group.

A total of 404 evaluable subjects, randomized in a 1:1 ratio to 2 treatment groups (202 subjects per treatment group), achieves at least 80% power to detect a non-inferiority margin of 1.606 in the hazard ratio, which corresponds to a 12% difference in the cumulative probability of failure rate between INI-based regimen group (37%) and PI-based regimen group (25%), with 97 events required. The sample size and power calculation assumes that the cumulative probability of failure is 25% for the PI regimen group and 23% for the INI-based regimen group (i.e. the expected hazard ratio is 0.909), using a non-inferiority margin of 1.606 in hazard ratio and a two-sided 95% confidence interval (CI). The sample size and power calculation were made using the statistical software package nQuery Advanced, non-inferiority testing of two survival curves using cox regression module (Version 8.1.2.0). With an estimated ~7.5% drop off rate/year, we plan to enroll 220 subjects per group to ensure we have sufficient power for this per-protocol analysis.

Superiority of INI-based regimen group versus PI-based regimen group will be evaluated after the non-inferiority is established. With an ITT analysis, 440 subjects and 78 events, a two-sided log-rank test at an alpha level of 0.05 will achieve at least 80% power to detect a 50% reduction in hazard rate in INI-based regimen (i.e. the hazard ratio is 0.5). A 50% reduction in hazard rate means that INI-based regimen could decrease the risk by 11.6% (25% for PI- vs 13.4% for INI- based regimen).

9.2 Planned recruitment rate

In the ANRS 146 OPTIMAL trial, in which similar patients were enrolled (late presenters with low CD4 cell count or ADE), 10% of screened patients were not eligible. Based on this information, we estimated that about 489 patients should be screened. Centres of NEAT ID Network with infectious disease units for inpatient and outpatient care will be the prioritised study sites of the LAPTOP Trial. We expect that about 45 sites in total across eight European countries. Therefore, we estimated that about 7-15 patients should be screened per site.

9.3 Statistical analysis plan

These analyses will assess the efficacy and safety of BIC containing regimen in comparison with the boosted PI containing regimen.

All randomised patients who received at least 1 time any study treatment will be included in the intent-to-treat (ITT) analysis population. Of note patients lost-to follow-up or violating the protocol will not be excluded from the ITT population. Patients who switch treatment to another will be analysed as if they are remained in their initial randomisation group. All participants who are lost to follow-up or discontinued the study when they are endpoint free at time of leaving the study will be censored at the time of leaving the study. We will use time-to-event methods, including Kaplan–Meier survival curves and Cox proportional-hazards models to account for all participants in the analysis. The per-protocol population will include all patients from the ITT population except those who did not fulfil the inclusion/exclusion criteria, who withdrew their consent, gave up, lost to follow-up or discontinued early study medication for any reasons other than any component of the primary endpoint.

9.3.1 Summary of baseline data and flow of patients

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation (SD), 1st quartile, median, 3rd quartile, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical variables.

The number of patients and the flowchart of the study will be presented. The period of enrolment and the total number of patients screened to be included in the study will be presented. The number of ineligible patients and the total number of randomised patients will be presented. The number of patients who never take the study treatment will also be presented by group and those who remained on the study treatment up to week 48 will be presented.

9.3.2 Primary outcome analysis

The primary outcome analysis will be performed with both ITT population and per-protocol population. The primary endpoint is the occurrence of a severe morbidity (virological failure; death related to HIV, AIDS, OI/severe BI or complications of therapy including IRIS; new ADE; new serious non-AIDS events; and clinically relevant AEs of any grade leading to study treatment discontinuation). The effect of study treatment will be assessed using Cox regression model with treatment group and adjustments for stratification factor (participating country and baseline CD4 cell counts). Separate analyses for each component of the primary endpoint will be done. Kaplan-Meier curves will be plotted for the primary endpoint and its component.

9.3.3 Secondary outcome analysis

All secondary outcome analysis will be done with the ITT population. The p-values will be two-tailed, with a significant level of 0.05.

The proportion of patients with HIV-ribonucleic acid (RNA) viral load <50 copies/mL at week 48 will be analysed using the snapshot approach. Fisher's exact test will be used to compare the estimated proportion between the two groups.

A genotypic resistance test will be performed in all patients with virological failure. Drugs resistance mutations will be identified from the International AIDS Society (IAS)-USA resistance testing panel (last version at the time of analysis) and for BIC we will use IAS, Agence Nationale de Recherches sur le SIDA (National Agency for AIDS Research) (ANRS) or Royal College of Physicians (RCP) lists to perform the analysis whenever they will be made available. Resistance to BIC will also be identified using

phenotypic resistance test. Fisher's exact test will be used to compare the presence of at least one drug resistance mutation between the 2 groups.

The median time to reach CD4 cell count >200/µl will be estimated using the Kaplan-Meier method, censoring at week 48 or last follow-up date if not seen at week 48. Time to reach CD4 cell count >200/µl will be defined as the time between the date of study treatment initiation (baseline, week 0) and the date of which patient reached CD4>200/µl. The log-rank test will be used to compare the two survival functions. The p-values will be two-tailed, with a significant level of 0.05. The proportion of patients with CD4 cell count <350/µl at week 48 will be done with the ITT population, with the last observation carried forward (LOCF) approach. Fisher's exact test will be used to compare the 2 groups.

The median change in CD4/CD8 ratio from baseline to week 48 will be analysed with the ITT population, with the LOCF approach. The non-parametric Mann Whitney test will be used to compare the change from baseline between the 2 groups.

The incidence of IRIS will be analysed with the Kaplan-Meier method. The Log-rank test will be used to compare the two survival functions. The effect of study treatment on IRIS will be assessed using Cox regression model with treatment group and adjustments for stratification factors.

The incidence of hospitalisation will be estimated by the Kaplan-Meier estimate. The Log-rank test will be used to compare the two survival functions. The duration of hospitalisation will be estimated by the cumulative days of hospitalisation during the course of study and will be compared between the 2 groups by using the Mann-Whitney test. The rate of relapse/recurrence will be estimated by the number of patients with relapse/recurrence divided by the total number patients in ITT population. Fisher's exact test will be used to compare the 2 groups.

The frequency of each Grade 2, 3 or 4 AEs, laboratory toxicities, and ART and OI/BI treatment changes and dose modifications due to toxicities and IRIS will be described and compared by group. Fisher's exact test will be used to compare the 2 groups.

The proportion of patients with health care resource use, and emergency room visits will be compared in the two groups with Fisher's exact test. The total inpatient days will be estimated by the cumulative inpatient days during the course of study and will be compared between the 2 groups by using the Mann-Whitney test.

To assess the impact of study treatment on the evolution of QOL at week 48, we will use multiple imputation approach to replace missing values. We will compare the treatment effect on QOL on each of the 5 datasets generated, including the imputed values, and the results will be combined with Rubin's rules. A generalized estimating equation (GEE) model will be used.

9.4 Subgroup analyses

Subgroup analyses for the primary endpoint will be done to explore whether estimated treatment effects vary significantly between subcategories of trial participants. The following variables will be assessed: age, gender, transmission group, ethnic group, baseline CD4 (<50, 50-199, ≥200), baseline viral load (<100,000, 100,000-500,000, >500,000), smoker, adherence (>/< 95%) and participating country. Heterogeneity of the treatment effect across subgroups will be assessed by including terms for interactions between treatment and subgroup variables in expanded Cox models. Age will be divided into three groups using tertiles/quartiles.

9.5 Interim analysis and criteria for the premature termination of the trial

No formal interim analysis will be done. However, a DSMB will be established and will review the data regularly during the course of the study (see Section 12 of the protocol for more details).

9.6 Subject population

All randomised patients who received at least 1 time any study treatment will be included in the ITT analysis population. Of note patients lost-to follow-up or violating the protocol will not be excluded from the ITT population.

The per-protocol population will include all patients from the ITT population except those who did not fulfil the inclusion/exclusion criteria, who withdrew their consent, gave up, lost to follow-up or discontinued study medication for any reasons other than study endpoint criteria.

9.7 Procedure(s) to account for missing or spurious data

To assess the impact of study treatment on the evolution of QOL at week 48, we will use multiple imputation approach to replace missing values. We will compare the treatment effect on QOL on each of the 5 datasets generated, including the imputed values, and the results will be combined with Rubin's rules. A GEE model will be used. LOCF approach will be used to replace missing CD4 and CD8 values.

9.8 Other statistical considerations

All deviations from the statistical analysis plan will be recorded during the conduct of the analysis. If there is a decision for major modifications to the statistical analysis while the clinical trial is in progress, this will be part of a protocol amendment.

10 DATA HANDLING

10.1 Data collection tools and source document identification

10.1.1 Source Data

Source data will be all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in the source documents (original records or certified copies) maintained at site.

10.1.2 Source Documents

Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial) will be maintained at site.

The subject's number and date of entry into the study, along with a study identifier, should be recorded in the subject's study records. The following should also be recorded in the study records; confirmation of written and verbal consent, the subject's clinical status, date of every study visit, date study medication was started and stopped, concomitant medications, copies of all relevant reports and laboratory tests, comments on results and reference to any AEs.

Source documents include, but are not limited to, participant medical records, SAE and reportable event forms (see section 8), questionnaires, laboratory reports, participant progress notes, pharmacy records and any other reports or records of procedures performed in accordance with the protocol.

10.1.3 Case report forms

Subject data collected during the study will be recorded in a web-based electronic CRF (eCRF). In order to maintain confidentiality, the subject information will be pseudo-anonymised.

The design of CRFs will ensure that:

- adequate collection of data has been performed
- proper paper trails can be kept to demonstrate the validity of the trial (both during and after the trial)
- only the data required by the protocol are captured in the CRF (using the CRF to capture secondary data not required for the study may be a criminal beach of the Data Protection Act, makes the CRF unnecessarily complicated, and can make it more difficult to extract the primary data for analysis)

Data required for the study will be recorded in an eCRF collection tool by appropriately trained and authorised member(s) of the study team who must be identified and authorised in writing by the PI before they conduct any study related tasks. A delegation of responsibility log identifying who can enter data and/or sign off a CRF will be maintained by the PI.

The eCRF should be kept current by entering data ideally within 7 working days of collection to enable the study monitor to review the subject status throughout the course of the study. In the case of the eCRF being unavailable, a paper CRF can be made available to use at site.

The data will be reviewed and approved by the Investigator following subject completion.

10.2 Data handling and record keeping

The Study Monitor and Data Manager will review data on an on-going basis and raise any discrepancies with site staff as required.

At the end of the study, the site will be provided with copies of their CRFs for filing in the ISF before the eCRF is decommissioned, ensuring site access to their data at all times.

Data extracted from the eCRF will be kept on a secure network drive of the sponsor with access to authorised personnel of the Biometrics Team only.

The data is pseudo-anonymised at all times and is transferred securely using an encrypted file share process. All transfers are fully documented.

10.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

10.4 Archiving

Following completion of the study, subject records, CRF and other study documentation will be retained by the Investigator in accordance with GCP and applicable regulatory requirements.

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g. for sponsor or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- The ISFs must be retained for a minimum of 5 years from the date of the final CSR. Sponsor will inform the investigator of the retention period due date at the time when this CSR (or equivalent) is issued to the site.
- The investigator must notify sponsor of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

Archiving will be authorised by the Sponsor following submission of the end of study report.

The sponsor will be responsible for archiving the Trial Master File (TMF). The Investigators at site(s) will be responsible for the retention/archiving of subject records, CRF, ISF and other study documentation (as applicable) in accordance with GCP and applicable regulatory requirements.

Destruction of essential documents will require authorisation from the Sponsor in writing.

The trial database will be maintained and stored in accordance with GCP.

11 MONITORING, AUDIT & INSPECTION

A risk-based monitoring plan will be followed for this study based on the trial risk assessment. The plan will detail monitoring frequency, requirements and processes.

The purpose of monitoring is to verify the rights and wellbeing of human subjects are protected; that trial data is accurate, complete and verifiable with source data; that the trial is conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

A monitor will conduct regular site visits for the purpose of monitoring various aspects of the study. The Investigator must agree to allow the study monitor and authorised representatives of the Sponsor, to inspect all CRF and corresponding source documents, e.g. original medical records, subject records and laboratory raw data, access to the clinical supplies, dispensing and storage areas and agree to assist with their activities if requested. The Investigator should provide adequate time and space for monitoring visits.

The monitor will query any missing or spurious data with the Investigator, which should be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, the monitor's signature and Investigator's or designee's confirmation signature.

For the purpose of compliance with GCP and regulatory agency guidelines, it may be necessary for sponsor authorised Quality Assurance personnel and/or authorised personnel from an external regulatory agency to conduct an audit/inspection of an Investigational site. The purpose of an audit

is to assess the quality of data with regard to accuracy, adequacy and consistency, and to assure that studies are in accordance with GCP, and Regulatory Agency guidelines. Having the highest quality data from studies is an essential aspect of drug development.

The Investigator will be given sufficient notice to prepare for such visits, which are planned to take usually between one and two days and may be conducted at any stage during the study. The audit will involve the review of all study related documentation, which is required by GCP to be maintained by each site, review of drug storage, dispensing and return, review of all study related supplies and review of source documents against the CRF to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AE which have occurred.

12 ROLES AND RESPONSIBILITIES OF TRIAL OVERSIGHT COMMITEES/ GROUPS & INDIVIDUALS

Three main trial management groups will be involved in the set up and management of the clinical trial.

Trial Steering Committee (TSC)

The TSC should meet to periodically review the safety data and will liaise with the DSMB regarding any safety issues. The TSC must have a majority independent representation, including the Chair.

Data Safety Monitoring Board (DSMB)

The DSMB is the group that monitors the main safety and efficacy outcome measures and the overall conduct of the trial, with the aim of protecting the safety and interests of the trial participants.

The DSMB will meet periodically to review blinded data. The frequency of these meetings will be detailed in a separate document, the DSMB Charter, but are planned to take place on a quarterly basis as a minimum.

Trial Management Group (TMG)

The TMG should meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them.

The membership, frequency and the study aspects to be reviewed by the above groups, will be outlined in a separate document.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC) review & reports

The study will comply with the following requirements

- Before the start of the trial, approval will be sought from an IRB/IEC for the trial protocol, ICFs and other relevant documents e.g. advertisements and GP information letters
- Substantial amendments that require review by IRB/IEC will not be implemented until the IRB/IEC grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the CAs before they can be implemented in practice at sites)

- All correspondence with the IRB/IEC will be retained in the TMF/ISF
- An annual progress report (APR) will be submitted to the IRB/IEC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- It is the CI's responsibility to produce the annual reports as required
- The CI will notify the IRB/IEC of the end of the study
- If the study is ended prematurely, the CI will notify the IRB/IEC, including the reasons for the premature termination
- Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the IRB/IEC

13.2 Peer review

The high-quality peer review process (initiated by study sponsor) for the trial protocol will meet the following review criteria:

a) **Independent**: At least two individual experts will review the study. Reviewers are external to the investigators' host institution and not involved in the study in any way.

b) **Expert**: Reviewers will have knowledge of the relevant discipline to consider the clinical and/or service-based aspects of the protocol, and/or have the expertise to assess the methodological and statistical aspects of the study.

c) **Proportionate**: Peer review commensurate with the size and complexity of the study.

13.3 Regulatory Compliance

This study will comply with the following:

- the trial will not commence until a Clinical Trial Authorisation (CTA) is obtained as required by local regulations
- the protocol and trial conduct will comply with the EU directive and local regulations applicable to each country

13.4 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the CI and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.5 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

The sponsor will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

13.6 Data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of the current Data Protection Regulations with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Personal information is to be collected, kept secure, and maintained in line with the following requirements:

- The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
- Secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media.
- Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.

13.7 Financial and other competing interests for the CI, PIs at each site and committee members for the overall trial management

The sponsor will identify and collect the following disclosure information:

- Ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- Commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- Any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

13.8 Indemnity

The Sponsor will undertake indemnity and insurance cover for this trial.

13.9 Amendments

The sponsor may make a non-substantial or substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the sponsor will submit a valid notice of amendment to the appropriate IRB/IEC, trial registries, and regulatory agencies. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial.

13.10 Post trial care

Post study medication will not be provided to participants. Following study completion patients will receive treatment as per local standard of care.

13.11 Access to the final trial dataset

The investigators will be provided reasonable access to statistical tables, figures, and relevant reports.

Sponsor will also provide the investigators with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with sponsor policies.

14 DISSEMINATION POLICY

Whole or part of this study results will be communicated, orally presented, and/or published in appropriate scientific journals. Full anonymity of subject's details will be maintained throughout. Subjects wanting to see the results of the trial can request a copy of the article from the investigators once it has been published.

Preliminary data review and analysis may be conducted on the main study cohort or a sub study cohort throughout the study duration and may be presented in scientific presentations in both national and international conferences and publication.

The data generated in the study will be submitted to a relevant medical journal according to criteria set out in The International Committee of Medical Journal Editors (www.icmje.org) who recommends that;

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
ii. Drafting the work or revising it critically for important intellectual content; AND
iii. Final approval of the version to be published; AND
iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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APPENDIX 1 - STUDY FLOWCHART

Procedures	Screening Visit	Baseline Visit	Treatment Phase						Follow Up/Early Termination Visit
	Day -28 to Enrolment[1]		Week 4 (± 7 days)	Week 8 (± 7 days)	Week 12 (± 7 days)	Week 24 (± 7 days)	Week 36 (± 7 days)	Week 48 (± 7 days)	30 days following Week 48 visit (± 7 days)
Informed consent	•								
Eligibility assessment[2]	•								
Demographics	•								
Medical and social history[3]	•								
ECG[4]	•								
HBV and HCV testing[5]	•								
TB test[6]	•								
Local Resistance testing [7]	•								•
Physical examination (including height & weight)[18]	•					•		•	
Randomisation		•							
Symptom-directed physical examination		•	•	•	•	•	•	•	•
Vital signs[8]	•	•	•	•	•	•	•	•	•
Urinalysis[9]	•	•	•	•	•	•	•	•	•
Haematology (including CD4 & CD8 testing)[10]	•	•	•	•	•	•	•	•	•
Clinical chemistry[11] (including urinary chemistry)	•	•	•	•	•	•	•	•	•
Viral load testing[12]	•	•	•	•	•	•	•	•	•
Sample collection for central resistance testing (deep sequencing)[13]		•	•	•	•	•	•	•	•
Concomitant medications	•	•	•	•	•	•	•	•	•
Adverse event assessments		•	•	•	•	•	•	•	•
Quality of Life questionnaire (EuroQoL EQ-5D-3L)		•	•	•	•	•	•	•	•
HIV Symptom Index questionnaire (HIV-SI/SDM)		•	•	•	•	•	•	•	•
Dispensing of trial drugs[14]		•			•	•	•		
Adherence[15]					•	•	•	•	
Serum pregnancy test[16]	•								
Urine pregnancy test[17]		•	•	•	•	•	•	•	•

	Assessment sub notes	Parameters/Notes
1	Screening visit	The maximum screening window is 28 days; however, participants should be invited for their baseline visit as soon as reasonably possible in order to start their treatment. The baseline resistance result is not required for eligibility or prior to randomisation.
2	Eligibility	According to the inclusion/exclusion criteria.
3	Medical & social history	Including: • Recreational drug use • Smoking history • Alcohol intake • Concomitant diseases • Past & present medical history, including HIV- associated conditions • Review of any medication taken within the last 30 days
4	ECG	12-Lead ECG performed supine
5	HBV & HCV testing	HBV antigen test and hepatitis C (HCV) antibodies test (if patient tests positive for HCV antibodies, test for HCV RNA, if positive and chronic for either HBV or HCV, add HBV DNA test at baseline visit). HBV test to be repeated in event of positive result. Participants with active HBV infection at study entry will be monitored throughout the study and additional HBV DNA tests performed at the Week 24 and 48 visits.
6	TB Testing	A TB test (IGRAs e.g. ELISPOT, QuantiFERON) will be performed in patients with expected latent TB at the screening visit. A TB test can be performed at subsequent visits on the basis of clinical suspicion.
7	Resistance testing (performed locally)	A local resistance test will be performed at the screening visit. This result is not required for eligibility or prior to randomisation. An additional resistance test will be performed at the ETV for patients with virological failure or insufficient virological response.
8	Vital Signs (10 mins resting)	Including: • Pulse • Blood pressure

	Assessment sub notes	Parameters/Notes
9	Urinalysis	Including: • Urinary creatinine* • Urinary glucose* • Urinary proteins* • Albumin* • Nitrites* • Albumin: Creatinine Ratio (ACR) and Protein: Creatinine Ratio (PCR) • Urinary phosphate • Beta-2 microglobulin • Leukocytes§ * Assessments should be performed as per local site procedure; however, assessments marked with an asterisk are mandatory for the study. § Baseline only
10	Haematology (non-fasting)	Including: • Platelet count* • RBC Count (indices MCV & MCH)* • WBC count (absolute)* • CD4 Count and %* • CD8 Count and %* • Haemoglobin* • Haematocrit* RBC Count indices: • MCV* • MCH* Automated WBC differentials: • Neutrophils* • Lymphocytes* • Monocytes* • Eosinophils* • Basophils* * Assessments should be performed as per local site procedure; however, assessments marked with an asterisk are mandatory for the study.

	Assessment sub notes	Parameters/Notes
11	Clinical chemistry (non-fasting)	• Urea* • Chloride* • Alkaline phosphatase* • Creatine phosphokinase* • Creatinine* • Calcium* • Phosphate* • Creatinine clearance, eGFR* (Calculations: Cockcroft-Gault (requires weight), MDRD, CX-Epi) • Glucose* • Total* and indirect bilirubin • Potassium* • Total protein* • Sodium* • ALT* • AST* • Albumin* • Cholesterol* • HDL* • LDL* • Triglycerides* * Assessments should be performed as per local site procedure; however, assessments marked with an asterisk are mandatory for the study.
12	Viral load testing	HIV RNA viral load
13	Resistance testing for deep sequencing (sent to central laboratory)	In addition to the resistance test performed locally, a resistance testing sample will be taken at the Baseline visit, each visit in the treatment phase (Week 4, 8, 12, 24, 36 and 48) and at the ETV (for patients with virological failure identified outside of a scheduled visit. All resistance testing samples for patients with virological failure will be sent to a central laboratory for next generation sequencing to look for low-level pre-existing resistance in cases of suspected resistance development.
14	Drug dispensing	There will be four dispensations of the study medication to the patient (Baseline visit, Week 12, 24 and 36).
15	Adherence	Also performed at the ETV if required.
16	Serum pregnancy test	For women of child bearing potential only (see Appendix 7 for definition).
17	Urine pregnancy test	Dipstick and urine pregnancy test (WOCBP only - see Appendix 7 for definition). This is a mandatory assessment.
18	Physical examination	For weeks 24 and 48, only a weight measurement is required

APPENDIX 2 – AIDS CLINICAL TRIAL GROUP (ACTG) GRADING SCALE

DAIDS AE Grading Table Corrected Version 2.1-July 2017

Attached as a separate document and available online at:
https://rsc.tech-res.com/docs/default-source/safety/daidsgradingcorrecetedv21.pdf?sfvrsn=6

APPENDIX 3 – AIDS-DEFINING CONDITIONS

From CDC, available at https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2.htm

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision) †
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii,* disseminated or extrapulmonary†
- *Mycobacterium tuberculosis* of any site, pulmonary, †§ disseminated, † or extrapulmonary†
- *Mycobacterium*, other species or unidentified species, disseminated† or extrapulmonary†
- *Pneumocystis jirovecii* pneumonia†
- Pneumonia, recurrent†§
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month†
- Wasting syndrome attributed to HIV

* Only among children aged <13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12].)

† Condition that might be diagnosed presumptively.

§ Only among adults and adolescents aged ≥13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17].)

APPENDIX 4 - INISIGHT SERIOUS NON-AIDS EVENTS CRITERIA

Version 4, August 2012

ACUTE MYOCARDIAL INFARCTION

A. Rise and/or fall of cardiac biomarkers (preferably troponin), with at least one value above 99th percentile of upper reference limit (URL)

B. Occurrence of a compatible clinical syndrome, including symptoms (such as chest pain) consistent with myocardial ischemia

C. ECG changes indicative of new ischemia (new ST-changes or new left bundle branch block [LBBB]), or development of pathological Q waves on the ECG

D. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

E. Sudden unexpected cardiac death involving cardiac arrest before biomarkers are obtained or before a time when biomarkers appear, along with (1) new ST-changes or new LBB, or (2) evidence of fresh thrombus on coronary angiography or at autopsy

F. In patients with percutaneous coronary interventions and normal baseline troponin, increases in troponin of three times the 99th percentile of URL

G. In patients with coronary artery bypass grafting and normal baseline troponin, increases in troponin of five times the 99th percentile of URL PLUS at least one of the following: (1) new pathological Q-waves or new LBBB, (2) angiographically documented new graft or native artery occlusion, or (3) imaging evidence of new loss of viable myocardium

H. Pathologic findings of acute myocardial infarction (including acute MI demonstrated as the cause of death on autopsy)

I. Development of 1) evolving new Q waves, or 2) evolving ST elevation, preferably based on at least 2 ECGs taken during the same hospital admission

J. In patients with coronary artery bypass grafting and normal baseline troponin, increases in troponin of five times the 99th percentile of URL

Confirmed: One of the following 5 criteria (adapted from 2007 Universal Definition of Myocardial Infarction):
1. A + (B or C or D)
2. E
3. F
4. G
5. H

Probable: B+I or J

CONGESTIVE HEART FAILURE

A. Clinical signs and symptoms compatible with left or right sided heart failure (e.g., paroxysmal nocturnal dyspnea, rales or S3 on auscultation, jugular venous distention) without an alternative explanation

B. Hemodynamic measurements, radionucleotide ventriculography, echocardiogram, cardiac catheterization, or multiple gated acquisition scan showing a decreased ejection fraction of < 45%

C. Echocardiogram, cardiac catheterization or other studies showing evidence of increased left atrial pressure or right heart failure

D. Elevated levels of Brain Natriuretic Peptide (BNP) or NT-proBNP

E. Chest x-ray or other imaging study showing evidence of congestive heart failure, including cardiac enlargement

F. Documentation of treatment for congestive heart failure

Confirmed: (A+B) or (A+C) or (A+D)
Probable: A+E+F

CORONARY ARTERY DISEASE REQUIRING DRUG TREATMENT

A written report in the medical record documenting:

A. Evidence of myocardial ischemia based on either diagnostic imaging (such as a stress echocardiogram or thallium scan) or diagnostic changes on an electrocardiogram (such as during stress testing or an episode of chest pain)

B. Evidence of coronary artery disease based on coronary angiography or other diagnostic imaging

C. Other evidence of myocardial ischemia and/or coronary artery disease (including that based primarily upon symptoms and clinical presentation, such as chest pain with exertion)

D. Use of medication given to treat or prevent angina (e.g., nitrates, beta blockers, calcium channel blockers)

Confirmed: (A or B) + D
Probable: C+D

CORONARY REVASCULARIZATION

Confirmed: A procedure report, hospital discharge summary, or other medical record from the hospitalization during which the procedure was performed for treatment of coronary artery disease (including coronary artery bypass graft, coronary artery stent implant, coronary atherectomy, and percutaneous transluminal angioplasty), or a consultation note from the participant's cardiologist documenting the occurrence of the procedure

Probable: Not applicable

DECOMPENSATED LIVER DISEASE

A. Histologic, radiographic, or ultrasound evidence of cirrhosis, as documented by one of the following:

1. Histologic evidence of cirrhosis obtained by liver biopsy or autopsy

2. MRI or CT consistent with cirrhosis
3. A positive result on transient elastography (FibroScan) or other ultrasound imaging consistent with cirrhosis

B. Clinical evidence of decompensation, as documented by one of the following, and without an alternative explanation:

1. Ascites
2. Hepatic encephalopathy
3. Bleeding from gastric or esophageal varices
4. Spontaneous bacterial peritonitis

Confirmed: A+B
Probable: B

DEEP VEIN THROMBOSIS

A. Diagnosis of deep vein thrombosis (DVT) by contrast venography, helical computed tomography, MRI, or ultrasonography other comparable imaging techniques

B. An elevated D-dimer test OR abnormal plethysmography

C. A score on the Wells Clinical Prediction Rule for DVT of ≥ 3 points

D. Absence of alternative diagnosis as likely or greater than that of deep venous thrombosis

Wells Clinical Prediction Rule for DVT
One point for each of the following:

- Active cancer (treatment ongoing or within previous 6 months, or palliative)
- Paralysis, paresis, or plaster immobilization of lower extremities
- Recently bedridden for more than 3 days, or major surgery, within 4 weeks
- Localized tenderness along distribution of the deep venous system
- Entire leg swollen
- Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)
- Pitting edema (greater in the symptomatic leg)
- Collateral superficial veins (non-varicose)

(Adapted from: Wells PS et al. Lancet 1997;350:1796)

Confirmed: A
Probable: B+C+D

DIABETES MELLITUS

A. Classic symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose concentration >=200 mg/dl (11.1 mmol/l). (Classic symptoms include polyuria and polydipsia; Random is defined as any time of day without regard to last meal)

B. 2-hour plasma glucose >=200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water).

C. Repeated abnormal fasting plasma glucose (FPG) and/or abnormal Haemoglobin A1C level (HA1C) results using the following criteria:

1. FPG >=126 mg/dl (7.0 mmol/l) on at least two different dates (Fasting is defined as no caloric intake for at least 8 hours).
2. HA1C >=6.5% on at least two different dates
3. An FPG >=126 mg/dl (7.0 mmol/l) PLUS a HA1C >=6.5%, with these tests performed on two different dates

D. Documentation of taking an approved anti-diabetic medication to lower glucose levels in the blood, such as insulin or oral hypoglycaemic agents.

E. A single abnormal FBS OR a single abnormal HA1C

Confirmed: A or B or C
Probable: D
Possible: E

END-STAGE RENAL DISEASE

A. Haemodialysis or peritoneal dialysis documented in a clinical note for a period of at least three months

B. A kidney transplant documented in a clinical note

C. Haemodialysis or peritoneal dialysis documented in a clinical note for a period of at least one month and up to the time of death in a patient who dies within three months after dialysis begins

Confirmed: A or B
Probable: C

NON-AIDS-DEFINING CANCER

A. Diagnosis of cancer other than lymphoma, Kaposi's sarcoma (KS), or invasive cervical cancer in an autopsy report

B. Diagnosis of cancer other than lymphoma, KS, or invasive cervical cancer in a pathology report that established the diagnosis

C. Diagnosis of cancer other than lymphoma, KS, or invasive cervical cancer in a hospital discharge summary or consultation note from the hospitalization or clinic visit during which the diagnosis was established

Confirmed: A or B
Probable: C

PERIPHERAL ARTERIAL DISEASE

A. Compatible clinical signs and symptoms (e.g., intermittent claudication, femoral bruit, decreased peripheral pulses, change in colour or temperature of limb suggesting peripheral arterial disease)

B. Positive results on diagnostic imaging studies (e.g., Doppler ultrasound, contrast arteriography, MRI arteriography)

C. Ankle Brachial Pressure Index < 0.90 in non-diabetics

D. A procedure report, hospital discharge summary, or other medical record from the hospitalization during which the procedure was performed documenting an invasive procedure for treatment of peripheral arterial disease (e.g., percutaneous transluminal angioplasty, endovascular procedures, or vascular surgery), or a consultation note documenting the occurrence of the procedure

Confirmed: (A+B) or (A+C) or D
Probable: A

PULMONARY EMBOLISM

A. Symptoms compatible with pulmonary embolism, such as shortness of breath, chest pain, or haemoptysis

B. Results consistent with a diagnosis of pulmonary embolism on pulmonary angiography, helical CT, ventilation-perfusion scan or other comparable imaging studies

C. A diagnosis of pulmonary embolism on autopsy
D. Results consistent with a diagnosis of deep venous thrombosis on venography, ultrasound, or other comparable imaging studies

E. A chest x-ray which, if performed, does not suggest an alternative aetiology for the symptoms described in criteria A

Confirmed: (A+B) or C
Probable: A+D+E

STROKE

A. Acute onset with a clinically compatible course, including unequivocal objective findings of a localizing neurologic deficit

B. CT or MRI compatible with diagnosis of stroke and current neurologic signs and symptoms

C. Stroke diagnosed as cause of death at autopsy

D. Positive lumbar puncture compatible with subarachnoid haemorrhage

E. Death certificate or death note from medical record listing stroke as cause of death

Confirmed: (A+B) or C
Probable: (A+D) or (A+E)

APPENDIX 5 - INSIGHT PROGRESSION OF HIV DISEASE CRITERIA

Version 2.0, September 2010

	CONFIRMED	PROBABLE
CONSTITUTIONAL DISEASE		
HIV wasting syndrome	None	A plus B plus C: (A) unexplained, involuntary weight loss >10% from baseline, (B) persistent diarrhea with > 2 liquid stools/d for > 1 month or weakness for > 1 month or fever for > 1 month, (C) tests for alternate causes of weight loss, such as cancer, TB, MAC, cryptosporidiosis or other specific causes of weight loss, if obtained, should be negative
INFECTIONS		
Aspergillosis, invasive pulmonary	A plus B plus C: (A) CXR abnormality compatible with aspergillosis, (B) invasive mycelia consistent with Aspergillus on lung biopsy, (C) positive culture from lung biopsy or sputum collected by any method	A plus B: (A) CXR abnormality compatible with aspergillosis, (B) invasive mycelia consistent with Aspergillus on lung biopsy or positive culture of lung tissue or positive culture of sputum collected by any method
Aspergillosis, other invasive	A plus B plus C: (A) compatible clinical course, (B) invasive mycelia consistent with Aspergillus on tissue biopsy or clinical evidence of infection, (C) positive culture from the affected tissue	A plus B: (A) clinical evidence of invasive infection, (B) invasive mycelia consistent with Aspergillus on tissue biopsy or positive culture at a normally sterile site (e.g., blood) apart from the involved tissue
Bartonellosis	A plus B: (A) Clinical or histologic evidence of bacillary angiomatosis or bacillary peliosis, (B) a positive culture or PCR for *B. quintana* or *B. henselae*	A plus B: (A) Clinical evidence of bacillary angiomatosis or bacillary peliosis, (B) positive silver stain for bacilli from a skin lesion or an affected organ
Candidiasis of bronchi, trachea, or lungs	Macroscopic appearance at bronchoscopy or autopsy plus microscopic evidence of yeasts or pseudo hyphae	None
Candidiasis, esophageal	A plus B: (A) Macroscopic appearance at esophagoscopy or autopsy, (B) microscopic evidence of yeasts or pseudo hyphae	A plus B plus C: (A) Recent onset of retrosternal pain or difficulty on swallowing, (B) a clinical diagnosis of oral candidiasis, endoscopic visualization of candidiasis and/or microscopic evidence of yeasts or pseudo hyphae from oropharyngeal mucosa, (C) clinical response to treatment

	CONFIRMED	PROBABLE
INFECTIONS (CONTINUED)		
Chagas disease (American trypanosomiasis) of the CNS	Histologic evidence obtained by brain tissue biopsy or autopsy	A plus B plus C plus D: (A) Focal, typically hemispheral neurological dysfunction with onset over several days or weeks; (B) enhancing focal lesion(s) with mass effect, and surrounding edema and contrast enhancement, typically located in greymatter; (C) serum antibodies to *T. cruzi*, (D) response to standard therapy with documented clinical or radiographic improvement (if radiography was done, it must be improved), or peripheral blood smear or CSF smear positive for *T. cruzi*
Coccidioidomycosis, disseminated or extrapulmonary	From tissue other than lung or hilum, A or B or C: (A) Microscopic demonstration of spherules, (B) positive culture, (C) antigen detection	None
Cryptococcosis, meningitis or extrapulmonary	From tissue other than lung or hilum, A or B or C or D: (A) microscopic demonstration of narrow based budding yeast, (B) for meningitis, if done, a positive CSF India ink test, (C) positive culture, (D) antigen detention	None
Cryptosporidiosis	Diarrhea for > 1 month and positive microscopy	None
CMV retinitis	Autopsy demonstration	Typical appearance on fundoscopy of discrete patches of retinal whitening, spreading along blood vessels, associated with vasculitis, hemorrhage and necrosis, confirmed by ophthalmologist
CMV radiculomyelitis	Autopsy demonstration	A plus B plus C plus D plus E plus F: (A) Loss of sensation, leg weakness, or decreased reflexes, (B) presentation over 3 days to 3 weeks, (C) CT, MRI or myelogram must be done and all imaging studies must not show a mass lesion, (D) CSF shows > 10 WBC with > 50% polymorphs, (E) CSF shows no other pathogen, (F) persistence of symptoms in the absence of CMV treatment, or elevated quantitative CMV in the CSF by PCR

	CONFIRMED	PROBABLE
INFECTIONS (CONTINUED)		
CMV meningoencephalitis	Autopsy or brain biopsy demonstration	A plus B: (A) Rapid < 4 weeks syndrome with progressive delirium, cognitive impairment and fever, (B) CT/MRI demonstration of periventricular abnormalities or elevated quantitative CMV DNA in the CSF by PCR
CMV, other disease	A plus B plus C plus D: (A) compatible illness, (B) histologic demonstration of inclusion bodies from affected tissue, (C) if done, detectible CMV antibodies, (D) if done, detectible CMV DNA or CMV antigen in blood	A plus B plus C plus D: (A) Compatible illness, (B) moderate to markedly high CMV antigen or CMV DNA in blood, (C) response to therapy, (D) if done, detectible CMV antibodies
HSV mucocutaneous ulceration	A plus B: (A) Ulceration for > 1 month, (B) histology, culture, PCR, or detection of antigen from affected tissue	A plus B: (A) Typical HSV ulceration for > 1 month, (B) response to an antiviral active against HZV unless resistance is demonstrated
HSV, bronchitis, pneumonitis, esophagitis, or other visceral disease	A plus B: (A) Compatible symptoms, (B) histology, culture, PCR, or detection of antigen from affected tissue	None
HZV, disseminated	A plus B: (A) multiple ulcerated lesions affecting at least 2 non-contiguous dermatomes, or with generalized cutaneous dissemination; or HZV involvement of the lung, liver, brain, or other internal organs (B) positive culture, PCR, or antigen assay from affected tissue	A plus B: (A) multiple typical ulcerated lesions affecting at least 2 non-contiguous dermatomes, or with generalized cutaneous dissemination (B) response to an antiviral active against HZV unless resistance is demonstrated
Histoplasmosis, disseminated or extrapulmonary	A plus B: (A) Compatible symptoms, (B) histology or culture or elevated blood or urine antigen levels	None
Isosporiasis	Diarrhea for > 1 month, plus microscopic identification of *Isospora belli*	None
Leishmaniasis, visceral	Compatible symptoms, plus microscopic identification of Leishmania	Compatible symptoms, plus a positive PCR test for Leishmania
Microsporidiosis	Diarrhea for > 1 month plus Microscopic identification of Microsporidia	None

	CONFIRMED	PROBABLE
INFECTIONS (CONTINUED)		
MAC and other mycobacterial disseminated disease	A plus B: (A) Fever, fatigue, anemia or diarrhea, (B) positive culture from blood, body fluids or tissue other than pulmonary, hilar or stool	A plus B plus C: (A) Fever, fatigue, anemia or diarrhea, (B) AFB or positive direct MAC PCR in blood, body fluids or tissue other than pulmonary, hilar or stool (C) no concurrent non-pulmonary TB
M. tuberculosis disease, pulmonary	A plus B: (A) Compatible symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) culture or PCR from sputum or bronchial lavage or lung tissue	A plus B plus C plus D: (A) Symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) abnormal chest X-ray, (C) AFBs seen in sputum or lavage or lung tissue but not grown in culture, (D) responds to treatment **POSSIBLE (pulmonary TB only)** A plus B plus C plus D: (A) Symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) abnormal chest X-ray compatible with pulmonary TB (such as upper lobe cavitation, pleural exudate), (C) No other etiology for pulmonary symptoms and signs identified, (D) Responds to anti-tuberculosis treatment
M. tuberculosis disease, extrapulmonary	A plus B: (A) Compatible symptoms, (B) culture or PCR from blood or affected tissue	A plus B plus C: (A) Compatible symptoms, (B) AFBs seen from affected tissue or blood (C) concurrent diagnosis of pulmonary TB or responds to treatment
Nocardiosis	Clinical evidence of invasive infection plus a positive culture from the affected tissue or blood	Clinical evidence of invasive infection plus microscopic evidence of bronchial weakly acid-fast organisms from the affected tissue
Penicillium marneffei, disseminated	Culture from a non-pulmonary site	Known presence in a *P. marneffei* endemic area plus characteristic skin lesions plus response to antifungal therapy for penicillosis

	CONFIRMED	**PROBABLE**
INFECTIONS (CONTINUED)		
PcP	A plus B: (A) compatible clinical syndrome, (B) microscopic or histological demonstration of *P. jirovecii* cysts in a pulmonary specimen	A plus B plus C plus D plus E: (A) dyspnea or cough, or fever progressive over > 1 week, (B) diffuse chest x-ray abnormality or, if on inhalational pentamidine, diffuse upper lung field abnormality, (C) evidence of hypoxia, (D) not suggestive of bacterial pneumonia (i.e., not purulent sputum or hemoptysis, no bacterial pathogen identified in blood or bronchial wash), (E) response to PcP treatment
Pneumocystis jirovecii, extrapulmonary	Compatible symptoms, plus microscopy	None
Pneumonia, recurrent bacterial, excludes: (a) post- obstructive pneumonias, including in those with intrapulmonary/bronchial lesions, (b) aspiration pneumonia, including in those with decreased consciousness levels, (c) nosocomial ventilator-associated pneumonias	Both pneumonia episodes must occur after enrollment and satisfy criteria (A) plus (B) plus (C). The recurrent pneumonia must also satisfy criteria (D) plus (E): (A) Signs and symptoms suggestive of bacterial pneumonia, (B) focal CXR abnormality compatible with bacterial pneumonia, (C) identification of a bacterial pathogen by positive blood culture, positive bronchoscopic sputum culture, detection of Legionella or pneumococcal antigen in urine or blood or diagnostic serologic findings, (D) the second pneumonia had onset of symptoms < 365 days after the first episode, (E) there is strong evidence that the first episode was cured such as an intervening clear CXR or absence of symptoms after > 1 month off antibacterials effective against pathogens commonly producing pneumonia	Both pneumonia episodes must occur after enrollment and satisfy criteria (A) plus (B). The recurrent pneumonia must also satisfy criteria (C) plus (D): (A) Signs and symptoms suggestive of bacterial pneumonia, (B) focal CXR abnormality compatible with bacterial pneumonia, (C) the second pneumonia had onset of symptoms < 365 days after the first episode, (D) there is strong evidence that the first episode was cured such as an intervening clear CXR or absence of symptoms after > 1 month off antibacterials effective against pathogens commonly producing pneumonia
PML (progressive multifocal leukoencephalopathy)	A or B: (A) positive histology, (B) compatible clinical and radiologic course and positive CSF PCR for JK virus	A plus B plus C: (A) Consistent symptoms, (B) brain image consistent with PML, (C) no response to toxo treatment or toxoplasma seronegative

	CONFIRMED	**PROBABLE**
INFECTIONS (CONTINUED)		
Rhodococcus equi disease	Clinical evidence of invasive infection plus microbiologic identification of the organism in the affected tissue or blood	None
Salmonella septicemia, recurrent	Both episodes must occur after enrollment and met criterion (A). The second episode must meet criteria (B) and C: (A) Positive blood or tissue culture, (B) the second septicemia had onset of symptoms < 365 days after the first episode, (C) the second septicemia must be due to a different Salmonella serotype or there must be strong evidence that the first episode was cured such as a negative blood culture off effective antibacterials for > 1 week or absence of symptoms off antibacterials for > 1 month	None
Toxoplasmosis of brain	Microscopy	A plus B plus C: (A) Symptoms of focal intracranial abnormality or decreased consciousness, (B) brain image consistent with lesion(s) enhanced by contrast, (C) positive toxoplasma serology or responds to treatment clinically or by scan
NEOPLASMS		
Cervical carcinoma, invasive	Histology (NOT carcinoma-in- situ)	None
Kaposi sarcoma, (mucocutaneous or visceral)	Histology	Highly typical appearance and persistence for > 1 month
Lymphoma, primary, of brain	Histology	Symptoms consistent with lymphoma plus at least one CNS lesion with mass effect plus lack of clinical and radiographic response to at least 2 weeks of treatment for toxoplasmosis
Lymphoma, Hodgkin's	Histology	None
Lymphoma, non-Hodgkin's, all cell types	Histology	None

	CONFIRMED	PROBABLE
NEUROLOGICAL		
HIV-related encephalopathy (including AIDS Dementia Complex)	None	Cognitive or motor dysfunction interfering with usual activity, progressive over weeks or months plus no other condition to explain the findings plus brain image obtained and suggests no other causes plus grade 2 or worse impairment in at least 2 domains by NARS (see below) excluding abnormal domains at trial entry. (For persons with abnormal domains at entry worsening by at least two grades meets criteria.)

Abbreviated NARS (Neuropsychiatric AIDS Rating Scale) Grading for HIV Encephalopathy

Adapted from: Price RW, Brew BJ. The AIDS dementia complex. J Infect Dis 1988; 158 (5): 1079- 83, and Hughes CP, Berg L, Danziger WL. A new clinical scale for the staging of dementia. Brit J Psych 1982; 140: 566-92.

NARS stage	Cognitive-Behavioral Domains					
	Orientation	**Memory**	**Motor**	**Behavior**	**Problem solving**	**Activities of daily living**
0.5	fully oriented	complains of memory problems	fully ambulatory slightly slowed movements	normal	has slight mental slowing	slight impairment in business dealings
1	fully oriented, may have brief periods of “spaciness"	mild memory problems	balance, co-ordination and handwriting difficulties	more irritable, labile or apathetic, withdrawn	difficulty planning and completing work	can do simple daily tasks, may need prompting
2	some disorientation	memory moderately impaired, new learning impaired	ambulatory but may require walking aid	some impulsivity or agitated behavior	severe impairment, poor social judgement, gets lost easily	needs assistance with ADLs
3	frequent disorientation	severe memory loss, only fragments of memory remain	ambulatory with assistance	may have organic psychosis	judgement very poor	cannot live independently
4	confused and disoriented	virtually no memory	bedridden	mute and unresponsive	no problem-solving ability	nearly vegetative

APPENDIX 6 – IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME GENERIC CRITERIA

(Revised 01/10/09)

From ACTG, available under https://actgnetwork.org/IRIS_Case_Definitions

1. **Initiation, reintroduction or change in antiretroviral therapy/regimen or therapy for opportunistic infections (OI).**

   AND

2. **[1]Evidence of:**

   a. **an increase in CD4+ cell count as defined by ≥50 cells/mm^3 or a ≥2- fold rise in CD4+ cell count, and/or**

   b. **decrease in the HIV-1 viral load of >0.5 log10 and/or**

   c. **weight gain or other investigator-defined signs of clinical improvement in response to initiation, reintroduction or change of either antiretroviral therapy/regimen or OI therapy.**

   AND

3. **Symptoms and/or signs that are consistent with an infectious or inflammatory condition.**

   AND

4. **These symptoms and/or signs cannot be explained by a newly acquired infection, the expected clinical course of a previously recognized infectious agent, or the side effects of medications.**
   AND

5. **For purposes of data collection, the infectious/inflammatory condition must be attributable to a specific pathogen or condition. A Clinical Events form should be completed 16 weeks (± 4 weeks) after initial report if diagnosis confirmed or changed from initial report**

[1] If the study participant is being evaluated for an inflammatory condition at a time that is <4 weeks after initiation, reintroduction or change in antiretroviral therapy/regimen or OI therapy, items 2a through 2c are not required.

Refer to the "Criteria for the Diagnosis of Specific Immune Reconstitution Inflammatory Syndromes (IRIS)" document for specific Opportunistic Infection (OI) and non-pathogen condition diagnosis criteria.

Criteria for the Diagnosis of Specific Immune Reconstitution Inflammatory Syndromes (IRIS)

IRIS Focus Group

Given the paucity of data for a clearly-defined immune reconstitution inflammatory syndrome for each opportunistic pathogen, the IRIS Working Group concentrated on developing specific definitions for the most well-characterized IRIS in the literature. IRIS events may occur as paradoxical worsening or as an unmasking. Paradoxical responses are described as an initial clinical worsening when patients are started on pathogen-specific therapy and/or ART simultaneously. Unmasking refers to aberrant clinical presentations of previously common OIs such as localized Mycobacterium avium *complex (MAC) lymphadenitis and* Cytomegalovirus *(CMV) vitritis occurring within the first weeks of starting ART suggesting that patients have sub-clinical disease prior to the initiation of ART. There are specific definitions including confirmed and probable for the following specific pathogen IRIS:* Mycobacterium avium *complex (MAC),* Progressive Multifocal Leukoencephalopathy *(PML),* Cytomegalovirus *(CMV),* Mycobacterium tuberculosis *(TB) and* Cryptococcus neoformans*. All other clinical syndromes attributed to immune reconstitution will be treated as probable IRIS events without specific definitions and will include* Pneumocystis jirovecii *pneumonia (PCP), Varicella Zoster (VZV), Herpes Simplex (HSV), Hepatitis B, Hepatitis C, Toxoplasmosis, Kaposi's Sarcoma, Graves' disease, Sarcoidosis, and other autoimmune disorders. For these less well-defined IRIS, key data will be captured on a generic form that includes clinical signs/symptoms, CD4, HIV RNA data, and clinical outcomes.*

Specific IRIS Case Definitions

1. ***Cytomegalovirus* (CMV): *{Ophthalmologic only}*** IRIS associated with CMV is fairly common; syndromes include uveitis, vitritis, extension or new development of retinal opacification, proliferative vitreoretinopathy (leading to retinal detachment), neovascularization, macular or optic nerve edema and subcapsular cataracts (leading to visual impairment) [1, 2]. The inflammatory component is marked, with significant anterior and/or posterior chamber inflammation. Vitritis and extension or new development of retinal opacification usually occurs within 3-12 weeks of beginning antiretroviral therapy/regimen and/or CMV antiviral therapy; uveitis may occur months to years after beginning antiretroviral therapy. Antiretroviral therapy/regimen is usually continued; some patients are also treated with anti-CMV drugs, especially those with sight-threatening disease. IRIS associated with gastrointestinal or neurologic (non-ocular) CMV disease have not be adequately characterized

   Confirmed CMV IRIS in patients *with* a prior history of CMV retinitis: previous CMV retinitis diagnosis by ACTG criteria and improvement of signs/symptoms with anti-CMV therapy, with the subsequent development of ocular inflammatory changes in uveovitreal tract, lens or retina, with or without associated visual changes, as documented by an experienced ophthalmologist.

   Confirmed CMV IRIS in patients *without* a prior history of CMV retinitis: the development of significant ocular inflammation in the uveovitreal tract, lens or retina attributed to CMV in the absence of ophthalmologic findings typical for acute CMV retinitis, with or without visual changes, as documented by an experienced ophthalmologist.

   Probable **CMV IRIS in patients *with* a prior history of CMV retinitis** previous CMV retinitis diagnosis by ACTG criteria and improvement of signs/symptoms with anti-CMV therapy, with the subsequent development of ocular inflammatory changes in uveovitreal tract, lens or retina, with or without associated visual changes, as documented by a non-ophthalmologist clinician

2. ***Cryptococcus neoformans***. The best described cases of *Cryptococcus neoformans* IRIS involve inflammatory changes developing in patients with recently diagnosed cryptococcal meningitis, cryptococcemia or pneumonia who have responded to appropriate antifungal therapy [1, 3,4]. Most have presented as meningitis, associated with CSF abnormalities (significantly elevated protein, lymphocytes, hypoglycorrhachia and cryptococcal antigen titers) with negative cultures. CNS imaging may demonstrate new meningeal inflammation. Significant elevations of intracranial pressure may occur. Non-CNS presentations are also common and have included the development of mediastinal or cervical adenopathy, necrotizing pneumonia, cavitation of previously documented pulmonary lesions, focal lymphadenitis and cutaneous abscesses. Biopsies may demonstrate granulomatous changes and cryptococci but typically cultures are negative. These presentations have occurred anywhere from two weeks to 11 months after initiation of antiretroviral therapy/regimen, with most cases occurring within three months. Less well described are cases of cryptococcal meningitis presenting only after initiation and response to antiretroviral therapy/regimen, also associated with elevated CSF cryptococcal antigen (CRAG) titers, negative CSF cultures and significant meningeal enhancement on scan.

   Confirmed cryptococcal IRIS in patients *with* a prior history of cryptococcosis: Cryptococcal meningitis or other diagnosis of systemic cryptococcal infection (fungemia, pneumonia) by ACTG criteria and improvement of signs/symptoms with antifungal therapy, with the subsequent development of new or worsening pulmonary infiltrates, new meningeal enhancement on scan or abnormal CSF findings (low glucose, elevated WBC, CSF CRAG with negative fungal culture), mediastinal or cervical lymphadenopathy, pleural effusion, cutaneous abscesses or cryptococcal lesions at other sites; histopathology from non-meningeal site demonstrating inflammatory changes and organisms in the absence of a positive culture or positive culture.

   Confirmed cryptococcal IRIS in patients *without* a prior history of cryptococcosis: the development of meningitis with meningeal enhancement on scan with abnormal CSF findings (low glucose, elevated WBC, positive CSF CRAG with negative or positive fungal culture), mediastinal or cervical lymphadenopathy, pleural effusion, cutaneous abscesses or cryptococcal lesions at other sites; histopathology from non-meningeal site demonstrating inflammatory changes and organisms in the absence of a positive culture or positive culture.

   Probable cryptococcal IRIS in patients* with *a prior diagnosis of cryptococcosis: *previous cryptococcosis diagnosis by ACTG criteria and improvement of signs/symptoms with anti-cryptococcal therapy, and the subsequent development of focal inflammatory site(s); histopathology from involved site or sterile body fluid analysis demonstrating inflammatory changes (e.g., granulomas, lymphocytes) in the absence of positive stains or cultures for any other pathogen or any non-infectious histopathologic diagnosis; and negative blood cultures for Cryptococcosis; and negative CSF CRAG if obtained or development of new onset CNS signs or symptoms with meningeal enhancement or other atypical radiographic changes with no evidence of other neurologic disease to explain the findings.*

   Probable cryptococcal IRIS in patients* without *a prior diagnosis of cryptococcosis: *the subsequent development of focal inflammatory site(s); histopathology from involved site or sterile body fluid analysis demonstrating inflammatory changes (e.g., granulomas, lymphocytes) accompanied by evidence consistent with cryptococcosis in the absence of positive cultures for any other pathogen.*

3. ***Mycobacterium avium* complex (MAC).** This is one of the best described IRIS. The most common presentation is focal lymphadenitis (especially cervical) with high fever, elevated WBC counts and negative blood cultures; fistula formation may occur. There is a significant inflammatory component on biopsy with necrotizing granulomas, caseation and AFB. The syndrome usually

occurs within 3-12 weeks of initiating antiretroviral therapy/regimen and/or anti-mycobacterial therapy**,** although rare cases have been described beyond 6 months with deep tissue foci, e.g. psoas abscess. MAC IRIS has presented as diffuse adenopathy, and as focal disease in diverse sites (paraspinous, mediastinal, abdominal, vertebral, pulmonary and CNS). [1,5,6]

Confirmed MAC IRIS in patients *with* a prior history of disseminated MAC (dMAC): previous disseminated MAC diagnosis by ACTG criteria and improvement of signs/symptoms with anti-MAC therapy, with the subsequent development of focal inflammatory site(s).

Confirmed MAC IRIS in patients *without* a prior history of dMAC: the development of focal inflammatory site(s); histopathology from the involved site demonstrating inflammatory changes (e.g., granulomas) accompanied by histologic or culture evidence of AFB consistent with MAC in the absence of positive cultures for any other AFB; and may have positive blood cultures for MAC.

Probable MAC IRIS in patients *with* a prior history of dMAC: previous dMAC diagnosis by ACTG criteria and improvement of signs/symptoms with anti-MAC therapy, and the subsequent development of focal inflammatory site(s); histopathology from involved site demonstrating inflammatory changes (e.g., granulomas) in the absence of positive stains or cultures for any other pathogen or any non-infectious histopathologic diagnosis; and negative blood cultures for MAC.

Probable MAC IRIS in patients *without* a prior diagnosis of MAC: the subsequent development of focal inflammatory site(s); histopathology from involved site demonstrating inflammatory changes (e.g., granulomas, lymphocytic infiltrates) and without evidence of any other specific pathogen (stains may be positive for AFB); and negative blood cultures for MAC.

4. ***Mycobacterium tuberculosis* (TB).** Tuberculosis-associated IRIS can present as one of two main syndromes: (1) a paradoxical reaction after the start of ART in patients receiving tuberculosis treatment ("paradoxical" tuberculosis-associated IRIS), or (2) a new presentation of tuberculosis that is "unmasked" in the weeks following initiation of ART with an exaggerated inflammatory clinical presentation or complicated by a paradoxical response ("unmasking" tuberculosis associated IRIS). A "paradoxical" response to anti-tuberculous therapy was described as far back as 1955 in patients initiating therapy. In the HAART era, IRIS associated with TB is common and occurs in approximately 8-43% and typically consists of new and persistent fever after starting antiretroviral therapy/regimen; worsening or emergence of intrathoracic adenopathy, pulmonary infiltrates or pleural effusions, *or* worsening or emergence of cervical nodes on serial exam or of other tuberculous lesions, such as skin and CNS. It usually occurs within the first 4 weeks of beginning antimycobacterial therapy with or without antiretroviral therapy/regimen but has been described as late as 9 months when the patient is smear-negative. Antiretroviral therapy/regimen can usually be continued, often with anti-inflammatory support; corticosteroids have been used in those with CNS lesions or who are critically ill [7-12].

   Confirmed TB IRIS in patients *with* a prior history of TB (paradoxical TB-associated IRIS): There are three components to this case-definition (adopted from Lancet Infect Dis 2008, reference 12):

   A) Antecedent requirements

   i) Diagnosis of tuberculosis: previous pulmonary (smear positive or smear-negative) or extrapulmonary TB diagnosis by ACTG criteria

AND

ii) Initial response with anti-TB therapy (i.e. stabilization or improvement of signs/symptoms with appropriate anti-TB therapy prior to initiation of ART)*. For example, there has been cessation or improvement of fevers, cough, night sweats).

* (Note: this does not apply to patients starting ART within 2 weeks of starting tuberculosis treatment since insufficient time may have elapsed for a clinical response to be reported)

(B) Clinical criteria

The onset of tuberculosis-associated IRIS manifestations should be within 3 months of ART initiation, re-initiation, or regimen change because of HIV treatment failure.

Of the following, at least one major criterion or two minor clinical criteria are required:

Major criteria

• New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement—e.g. tuberculous arthritis

• New or worsening radiological features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI)

• New or worsening CNS tuberculosis (meningitis or focal neurological deficit; e.g. caused by tuberculoma)

• New or worsening serositis (pleural effusion, ascites, or pericardial effusion)

Minor criteria

• New or worsening constitutional symptoms such as fever, night sweats, or weight loss

• New or worsening respiratory symptoms such as cough, dyspnea, or stridor

• New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) Alternative explanations for clinical deterioration must be excluded

• Failure of tuberculosis treatment because of tuberculosis drug resistance

• Poor adherence to tuberculosis treatment

• Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed)

• Drug toxicity or reaction

Confirmed TB IRIS in patients *without* a prior history of TB (ART "unmasking" TB-associated IRIS): Patient is not receiving treatment for TB when ART is initiated. Active TB is diagnosed after initiation of ART and the diagnosis of TB fulfils ACTG criteria for smear-positive pulmonary TB, smear-negative pulmonary TB or extrapulmonary TB. Active TB develops within 3 months of starting ART and one of the following criteria is met: heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component. For

example, presentations may include TB lymphadenitis or TB abscesses with prominent acute inflammatory features; the development of pulmonary* or extrapulmonary TB with no evidence of miliary disease accompanied by marked focal inflammation; or histopathology from involved site demonstrating inflammatory changes (e.g., granulomas, caseation) accompanied by histologic or culture evidence of AFB consistent with TB in the absence of positive cultures for any other AFB.

Probable TB IRIS in patients *with* a prior history of TB: "Probable" status should be assigned for cases where criteria A and B are met (see confirmed TB IRIS with a prior history of TB definition) but an alternative diagnosis or explanation for clinical deterioration cannot be fully excluded.

Probable TB IRIS in patients *without* a prior diagnosis of TB: Patient is not receiving treatment for TB when ART is initiated. Active TB is diagnosed after initiation of ART and the diagnosis of TB fulfils ACTG criteria for smear-positive pulmonary TB, smear-negative pulmonary TB or extrapulmonary TB. There is heightened intensity of clinical manifestations but there is not clear evidence of a marked inflammatory component to the presentation or the subsequent development of focal inflammatory site(s) is beyond 3 months of ART initiation.

5. ***Progressive Multifocal Leukoencephalopathy* (PML)**. Inflammatory responses to PML usually occur within 3 months of beginning antiretroviral therapy. Based on available data, the simultaneous diagnosis of PML and IRIS post-HAART initiation is more commonly observed (i.e. unmasking IRIS). Furthermore, it appears that paradoxical worsening PML IRIS is identified sooner (within 4 weeks) than unmasking PML IRIS. MRI with gadolinium shows contrast enhancement suggesting an inflammatory response, and biopsy reveals significant inflammation with gliosis, marked intraparenchymal and perivascular infiltration by macrophages and lymphocytic infiltrates (especially CD8 T cells), giant cells, with or without demyelination. Intense JC-specific PCR signals (or other immunoreactivity to papovavirus antigens) are detected in brain tissue even in the absence of positive JC CSF PCR. The clinical responses are mixed: some improve, and some have significant worsening with progression to death. A variable response to steroids has been described [1,13,14].

   Confirmed PML IRIS in patients *with* a prior history of PML: previous PML diagnosis by ACTG criteria (consistent CT or MRI scan with positive biopsy or positive CSF JC PCR and the absence of any alternative diagnosis), with the subsequent development of new or worsening CT or MRI findings with contrast enhancement; brain biopsy shows focal inflammatory changes accompanied by histologic or PCR evidence of PML in the absence of another diagnosis.

   Confirmed PML IRIS in patients *without* a prior diagnosis of PML: the development of new neurologic deficit(s) in patient with no previously recognized CNS infection or malignancy, accompanied by CT or MRI changes showing contrast enhancement; brain biopsy shows focal inflammatory changes accompanied by histologic or PCR evidence of PML in the absence of another diagnosis.

   Probable PML IRIS in patients *with* a prior history of PML: previous PML diagnosis by ACTG criteria (consistent CT or MRI scan with positive biopsy or CSF JC PCR and the absence of any alternative diagnosis), with the subsequent development of new or worsening CT or MRI findings with contrast in the absence of another diagnosis.

Probable PML IRIS in patients *without* a prior diagnosis of PML: the development of new neurologic deficit(s) in a patient with no previously recognized CNS infection or malignancy accompanied by CT or MRI changes showing contrast enhancement consistent with PML with no brain biopsy obtained. CSF findings cannot be attributable to another pathogen or disease process.

IRIS Diagnoses without Specific Case Definitions

Pathogen-Directed:

1. ***Kaposi's Sarcoma* (KS*).*** Rapid KS progression [15] and local swelling with adjacent lymphadenopathy [20] have both been reported as a manifestation of immune reconstitution after antiretroviral therapy/regimen initiation. Whereas the latter syndrome may truly represent an IRIS syndrome, if there is no clear evidence of any characteristic inflammatory component [1, 16], then the progression could be due to a failure to reconstitute KSHV-specific immune responses. KS-IRIS is defined as a sudden or more dramatic progression of disease than expected as part of natural history that occurs within 12 weeks of initiation of ART. ART alone should be continued for 4-6 weeks to monitor for clinical response. If the lesions stabilize, have a regression of inflammation or lesion number or size diminishes, this will be defined as IRIS. Should disease progression continue, then this is unlikely to be IRIS and should be defined as progression of disease and managed with appropriate KSHV specific therapies. The presence of inflammation on biopsy may assist in distinguishing progression of disease vs. IRIS.

2. **Hepatitis B and C.** *Significant increase in ALT over baseline (flares) have been documented after beginning antiretroviral therapy/regimen with HBV co-infection as well as after interruption of antiretroviral therapy/regimen (especially in patients with HBV on a 3TC- or tenofovir-containing regimen). After immune recovery HBV "flares" may occur if HBV is not being concomitantly treated, although there are other potential reasons to consider. These include:*

a) spontaneous HBeAg seroconversion;

b) treatment induced exacerbation of the underlying disease;

c) hepatotoxic effects of treatment;

d) withdrawal of active HBV drug;

e) development of resistance and return of replication, and/or

f) superimposed and unrelated acute liver disease (e.g. hepatitis A)

Liver biopsy may be helpful in determining evidence of drug related (eosinophilic infiltrate) vs. acute viral hepatitis (hepatocyte swelling with lobular inflammation).

Biopsy may also grade and stage chronic viral hepatitis. IRIS is less well-defined in HCV co-infection, and increases in liver enzymes on antiretroviral therapy/regimen may be multifactorial as well.

3. **Herpes simplex virus *(HSV).*** *The development of unusual presentations of HSV following the initiation of antiretroviral therapy/regimen attributed to immune reconstitution have been rarely described.*

Localized HSV vesicles may occur within 8 weeks of initiating ART among persons with no prior history and no new source contact to attribute it to. Symptoms and signs are frequently consistent with a primary infection. Chronic erosive or ulcerative lesions of the genitals have been described in individuals who had prior histories of genital HSV. The appearance and clinical course of the lesions attributed to immune reconstitution appeared inconsistent with these patients' previous HSV presentations. Proctitis has also been reported [1,18,19]. Routine viral cultures may or may not yield HSV though histochemistry studies may show evidence of HSV antigens in the absence of a positive viral culture. Histopathology in some cases may demonstrate an inflammatory infiltrate with unusual prominence of plasma cells and eosinophils. Response to antivirals appears to be variable.

4. ***Pneumocystis jirovecii pneumonia*** **(PCP).** Despite being the most common OI with a relatively high CD4 threshold for development, few clear cases of Pneumocystis pneumonia IRIS have been documented so far (likely because steroids have been established for the use of severe PCP). Cases have been described as worsening of pneumonia and even respiratory failure, although the patients reported received suboptimal courses of steroids [20]. To entertain a diagnosis of PCP IRIS, bronchoscopy should rule out an intercurrent pulmonary process.

5. **Syphilis*.*** *New reactive RPR within 12 weeks of starting ART in setting of known previously treated syphilis and documented nonreactive within past 2 years without new attributable source. May also present serologically as less than or equal to 4-fold change in titer in someone with previous history of treated syphilis and no new attributable source. May present with systemic symptoms including arthralgia. May improve with anti-inflammatories.*

6. ***Toxoplasmosis*****.** There is also a very small database for possible toxoplasmosis IRIS. No specific clinical pattern has been seen, and there is no clear evidence of an inflammatory component.

7. ***Varicella Zoster*** **(VZV).** The development of herpes zoster after initiation of antiretroviral therapy/regimen has been attributed to immune reconstitution. The incidence of zoster appears to be 2- to 5-fold greater in those receiving antiretroviral therapy/regimen compared to those not receiving antiretroviral therapy/regimen. Most cases occur in the first 16 weeks following initiation of antiretroviral therapy/regimen. Those with higher percentage of CD8+ lymphocytes at the time of initiation of HAART and at one month following antiretroviral therapy/regimen appeared to be at higher risk for zoster [21]. Most cases present as cutaneous dermatomal disease or mucocutaneous disease, are mild, occur without systemic symptoms and respond to antiviral therapy. Iritis and keratitis have been described rarely [1,22]. It is not clear that cutaneous zoster following initiation of antiretroviral therapy/regimen has a significant inflammatory component that differentiates this from routine VZV.

8. **Other viral dermatose**s. Eruptive onset of new common warts, flat warts, or epidermodysplasia verruciformis-type warts, or inflammation/rapid growth of previously stable cutaneous or genital warts, have been noted during immune restoration [23-24]. In addition, eruptive onset of new molluscum contagiosum or inflammation/enlargement of pre-existing mollusca during immune restoration has been described [25].

Non-Pathogen or Unknown Pathogen Directed

1. ***Autoimmune disorders*****.** Systemic lupus erythematosus, polymyositis, rheumatoid arthritis, relapsing polychondritis and Guillain-Barre have also been attributed to immune reconstitution following administration of antiretroviral therapy/regimen [1,26].

2. ***Follicular inflammatory eruptions***. Sudden onset of follicular papulopustular inflammatory eruptions resembling acne vulgaris or acne rosacea have been reported within first 4 months of immune reconstitution [27]. Eosinophilic folliculitis, distinguished from acneiform eruptions by intense pruritus, an urticarial appearance to the papules, and histopathology showing follicular inflammation containing eosinophils, has been documented. An increased incidence of eosinophilic folliculitis has been noted in the first 6 months of HAART therapy [28].

3. ***Graves' Disease***. New onset of clinically significant Graves' disease (hyperthyroidism) has been reported following the initiation of antiretroviral therapy/regimen. The development of anti-thyrotropin receptor antibodies in individuals following antiretroviral therapy/regimen, not present before antiretroviral therapy/regimen initiation has been described [1, 26].

4. **Sarcoidosis.** *Worsening of previously diagnosed sarcoidosis or newly diagnosed sarcoidosis following antiretroviral therapy/regimen has been reported. Pulmonary involvement as well as extrapulmonary involvement (erythema nodosum) has been described [1, 26].*

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APPENDIX 7 – HIGHLY EFFECTIVE METHODS FOR AVOIDING PREGNANCY IN FEMALES OF CHILD BEARING POTENTIAL*

The following is the all-inclusive list of the highly effective methods for avoiding pregnancy (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).

The list does not apply to females of child bearing potential (FCBP) with same sex partners, when this is their preferred and usual lifestyle.

- True abstinence from penile-vaginal intercourse, when this is in line with the preferred and usual lifestyle of the subject [Hatcher, 2007a] (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception].
- Non-hormonal Intrauterine device or non-hormonal intrauterine system that meets the effectiveness criteria as stated in the product label [Hatcher, 2007a]
- Male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a]. The information on the male sterility can come from the site personnel's: review of subject's medical records; medical examination of the subject and/or semen analysis; or interview with the subject on his medical history.
- Combined (oestrogen and progesterone containing) hormonal contraception associated with the inhibition of ovulation***:
    - Oral
    - Intravaginal
    - Transdermal
- Bilateral tubal occlusion

[a] Nonoxynol-9 is the critical component in most spermicides and is regarded as an acceptable spermicidal agent. Concern has been raised that nonoxynol-9 damages the epithelial lining of the vagina, and exposure may facilitate transmission of viruses, particularly HIV. The World Health Organization conducted a technical consultation in October 2001 and concluded that the increased risk for such transmission was low to minimal [WHO/CONRAD, 2003].

* A Woman of childbearing potential (WOCBP) is defined as any female who has:

- Experienced menarche
- Not undergone surgical sterilization (hysterectomy , bilateral salpingectomy or bilateral oophorectomy)
- Not experienced menopause. Women are considered menopausal if they have not had a menses for at least 12 months and have an FSH (follicle stimulating hormone) of greater than 40 IU/L or, if FSH testing is not available, they have had amenorrhea for 24 consecutive months**.

**Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level.

***If a patient is randomised to Symtuza, an alternative highly effective method of contraception should be used

APPENDIX 8 – SAFETY REPORTING FLOW CHART

Safety Data	Reporting Format	Timelines
All SAEs arising during the Clinical Trial, regardless of Investigator/designee causality assessments against IMP(s)	SAE form	Site to report to sponsor within 24 hours of first becoming aware of the event. Sponsor to report to Funder within 24 hours of awareness.
Pregnancy information for all female Clinical Trial Subjects who become pregnant while participating in the Clinical Trial and following exposure to an IMP. The subject will also be followed to determine the outcome of the pregnancy (including information on the status of the mother and child), which will also be reported to sponsor.	Copies of the original Pregnancy CRF pages	Site to send to sponsor within 24 hours of first becoming aware of the pregnancy or the pregnancy outcome. Sponsor to report to Funder within 24 hours of awareness.
Deaths	Any AE, AR or unexpected AR that results in death should be reported as an SAE on an SAE form.	Site to report to sponsor within 24 hours of first becoming aware of the event. Sponsor to report to Funder within 24 hours of awareness.
Overdose	If the overdose fits the criteria of an SAE (see Section 8) it should be reported appropriately on an SAE form, else report as a Special Reporting Situation.	Site to report to sponsor within 24 hours of first becoming aware of the event. Sponsor to report to Funder within 24 hours of awareness.
Special Reporting Situations: (See section 8.10)	Email	Site to report to sponsor within 24 hours of first becoming aware of the event. Sponsor to report to Funder within 24 hours of awareness.
Product Quality Complaints	Email	Site to report to sponsor within 24 hours of first becoming aware of the event. Sponsor to report to Funder within 24 hours of awareness.

APPENDIX 9 – AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

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An Open-Label, Multi-Centre, Randomised Study to Investigate Integrase Inhibitor Versus Boosted Protease Inhibitor Antiretroviral Therapy for Patients with Advanced HIV Disease

-The Late Presenter Treatment Optimisation Study (LAPTOP)-

Version 5.0 dated 11 MAR 2024

SPONSOR: NEAT ID Foundation

Sponsor code: NEAT44

EudraCT: 2018-003481-13

EUCT: 2023-505167-36-00

PLEASE RETAIN ONE COPY FOR THE SITE FILE

Private & Confidential

GCP Compliance Statement:
This trial will be conducted in compliance with the protocol, the principles that have their origin in the Declaration of Helsinki and all applicable regulatory requirements

SPONSOR AND CHIEF INVESTIGATOR SIGNATURE PAGE

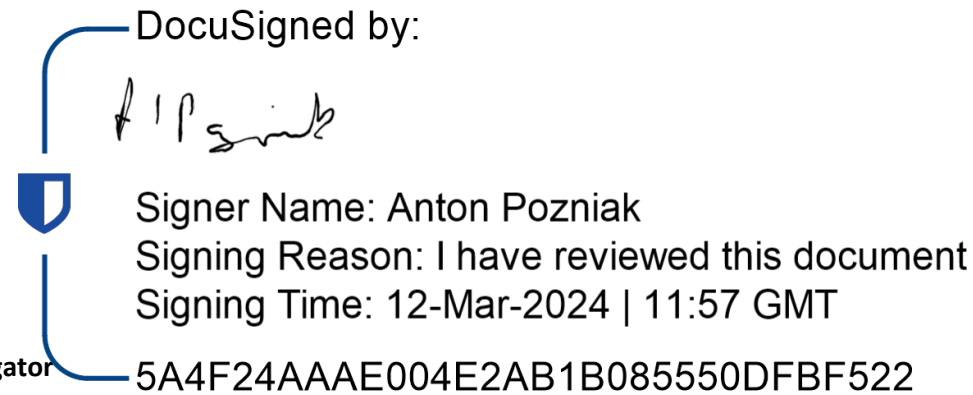
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) , Clinical Trial Regulation (EU) No 536/2014 and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

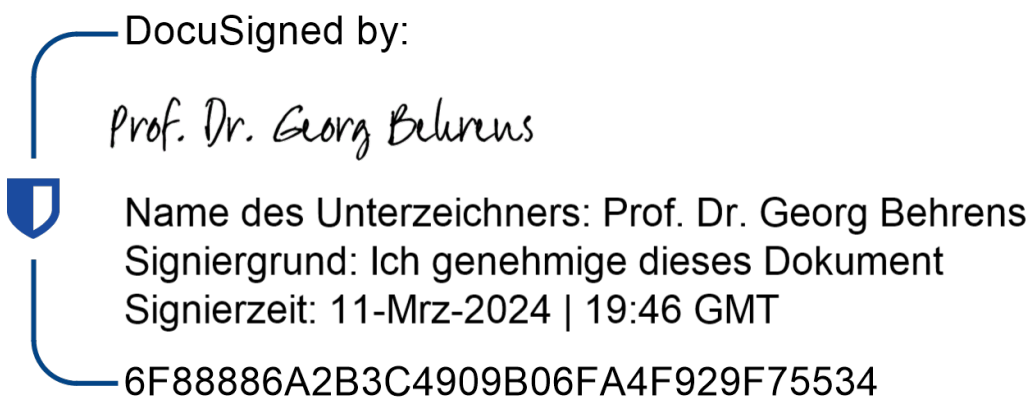
For and on behalf of the trial sponsor

Signature:



Chief Investigator

Signature:



STATISTICIAN OR STUDY ANALYST SIGNATURE PAGE

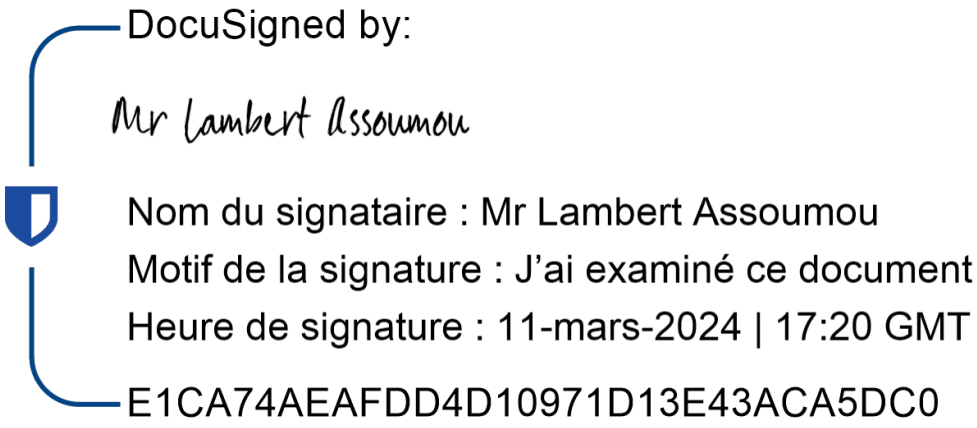
The undersigned confirm that the following protocol has been agreed and accepted and that the Statistician or Study Analyst agrees to conduct the trial in compliance with the approved protocol, Statistical Principles for Clinical Trials, ICH E10 and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928), Clinical Trial Regulation (EU) No 536/2014 and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's SOPs and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Statistician or Study Analyst

Signature:



PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the trial in accordance with ICH-GCP and the applicable regulatory requirements and with the approved protocol.

I agree to comply with the procedures for data recording/reporting

I agree to permit monitoring, auditing and inspection at this site and to retain all trial related essential documentation for the duration of the study as required according to ICH-GCP.

Principal Investigator:

Signature: _____ Date: ____ / _____ / _____

Name (print): _____

TABLE OF CONTENTS

KEY TRIAL CONTACTS

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FUNDING AND SUPPORT

FUNDERS/COLLABORATORS
Gilead Sciences, Inc. 333 Lakeside Drive Foster City CA 94404
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STUDY SYNOPSIS

Full Study Title	An Open-Label, Multi-Centre, Randomised Study to Investigate Integrase Inhibitor Versus Boosted Protease Inhibitor Antiretroviral Therapy for Patients with Advanced HIV-Disease
Short Title/Acronym	LAPTOP (The Late Presenter Treatment Optimisation Study)
Clinical Phase	IIIb
Trial Design	International, multi-centre, randomised, open-label, controlled study comparing two strategies for HIV-1 infected patients with advanced disease. Randomisation 1:1 into two arms, 48 weeks, stratified according to country and baseline CD4 cell count (<50 cells/µL, 50-199 cells/µL, or ≥200 cells/µL).
Name of Investigational Product	Treatment Arm 1 Bictegravir (50mg)/emtricitabine (200mg)/tenofovir alafenamide (25mg) [1 pill administered orally once daily for 48 weeks without regard to food] Treatment Arm 2 (Comparator Arm) Darunavir (800 mg)/cobicistat (150 mg)/emtricitabine (200 mg)/tenofovir alafenamide (10mg) [1 pill administered orally once daily for 48 weeks with food]
Trial Participants Population	HIV-1 infected patients ≥ 18 years and ART-naïve prior to enrolment.
Planned Sample Size	440 (220 subjects per treatment arm)
Key Eligibility Criteria	Subjects who meet the following eligibility criteria: 1. Ability to understand and sign a written informed consent form (ICF) and must be willing to comply with all study requirements 2. ≥ 18 years 3. HIV-1 infected AIDS except active tuberculosis (TB) or cryptococcal meningitis with any CD4 cell count, or; severe bacterial infection (BI) and must have a CD4 cell count < 200/µL within 28 days prior to study entry, or; any symptoms or no symptoms with CD4 cell count < 100/µL within 28 days prior to study entry and must have an entry HIV viral load > 1000 copies/mL, or; currently being treated for opportunistic infections (OI) 4. Have an entry HIV viral load > 1000 copies/mL 5. Able to take oral medications 6. ART-naïve prior to study enrolment 7. Willing to use acceptable methods of contraception
Treatment duration	48 weeks
Follow up duration	30 days
Formulation, Dose, Route of Administration	Subjects will be randomised in a 1:1 ratio into one of two treatment arms: Group 1 Integrase inhibitor containing regimen Bictegravir (50 mg)/emtricitabine (200 mg)/tenofovir alafenamide (25mg) [1 pill administered orally once daily without regard to food for 48 weeks] Group 2

	Boosted protease inhibitor regimen Darunavir (800 mg)/cobicistat (150 mg)/emtricitabine (200 mg)/tenofovir alafenamide (10mg) [1 pill administered orally once daily with food for 48 weeks]	
Indication	ART-naïve HIV-1 infected patients	
Methodology	Eligible consented patients will be randomised in a 1:1 ratio	
Number of sites	Up to 61 sites, in up to 11 countries	
Objectives	**Primary** To demonstrate the non-inferiority of an INI containing regimen [bictegravir (B)/emtricitabine (F)/tenofovir alafenamide (TAF) QD] versus a boosted PI regimen [darunavir (D)/cobicistat (C)/emtricitabine (F)/tenofovir alafenamide (TAF) QD] in patients with advanced HIV infection.	**Secondary** To investigate the immunological and virological response, tolerability, resistance development, discontinuation of therapy due to tolerability, QOL and IRIS incidence.
Outcome Measures	**Primary** 1. Time to failure, as the first occurrence of specified virological or clinical reasons.	**Secondary** 1. Proportion of patients with HIV-RNA viral load < 50 copies/mL at week 24, 36, 48 2. HIV-1 drug resistance at confirmed virological failure (genotype) 3. Time to reach CD4 count > 200/µL 4. Proportion of patients with CD4 cell count <200 and < 350µL at week 4, 8, 12, 24, 36, 48 5. CD4/CD8 ratio at week 4, 8, 12, 24, 36, 48 6. Incidence of IRIS in the two arms through week 48 7. Incidence and duration of hospitalisation, rate of relapse of specific OI/BI through week 48 8. Safety and tolerability, measured by Grade 2, 3 and 4 signs and symptoms and laboratory toxicities through week 48 9. ART and OI/BI treatment changes and dose modifications due to toxicities and DDI with ART, and IRIS through week 48 10. Health care resource use, including total inpatient days and emergency room visits through week 48 11. QOL and functional status outcomes, including overall self-reported QOL and functional status compared in the two groups at week 48

12. Discontinuation or modification of study medication due to insufficient virological response, resistance mutations at baseline, or resistance mutation development before week 48

LIST OF ABBREVIATIONS

Acronym	Description
3TC	Lamivudine
ABC	Abacavir
ACTG	AIDS Clinical Trial Group
ADE	Adverse Drug Event
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
ANRS	Agence Nationale de Recherches sur le SIDA (National Agency for AIDS Research)
AR	Adverse Reaction
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
B/BIC	Bictegravir
BI	Bacterial Infection
BMD	Bone Mineral Density
C	Cobicistat
CA	Competent Authority
CDC	Centres for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Chief Investigator
CI	Confidence Interval
CRF	Case Report Form
CTA	Clinical Trial Authorisation
D/DRV	Darunavir
DDI	Drug-Drug Interaction
DIBD	Developmental International Birth Date
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
DTG	Dolutegravir

EACS	European AIDS Clinical Society
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ELISPOT	Enzyme-Linked ImmunoSpot
ETV	Early Termination Visit
EU	European Union
EudraCT	European Clinical Trials Database
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FTC/F	Emtricitabine
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type-1
IAS	International AIDS Society
IB	Investigator's Brochure
IBI	Invasive Bacterial Infection
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assays
IMP	Investigational Medicinal Product
INI	Integrase Inhibitor
INSTI	Integrase Strand Transfer Inhibitor
IRB	Institutional Review Board
IRIS	Immune Reconstitution Inflammatory Syndrome
ISF	Investigator Site File
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NNRTI	Non-Nucleoside Reverse-Transcriptase Inhibitor
NRTI	Nucleoside Reverse-Transcriptase Inhibitor
OI	Opportunistic Infection
PBMC	Peripheral Blood Mononuclear Cells

PI	Principal Investigator
PI	Protease Inhibitor
QD	quaque die (once daily)
QOL	Quality of Life
QP	Qualified Person
RAL	Raltegravir
RNA	Ribonucleic Acid
RSI	Reference Safety Information
RT	Reverse Transcriptase
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	Tenofovir Alafenamide Fumarate
TDF	Tenofovir Disoproxil Fumarate
TB	Tuberculosis
TFV	Tenofovir
TMG	Trial Management Group
TMF	Trial Master File
US	United States
USM	Urgent Safety Measure

1. BACKGROUND AND RATIONALE

Treatment responses to antiretroviral therapy (ART) have constantly improved. This is due to novel compounds and combinations with improved antiviral efficacy and side effect profiles resulting in less virologic failures and treatment discontinuation. On the other hand, most recent randomised controlled trials for first line treatment consider patients with less advanced disease (mean CD4 cell counts at baseline >350/µl, less than 15% of patients with CD4 cell counts <200/µl) and low baseline viral loads [DeJesus et al., Raffi et al., Walmsley et al., Sax et al, Gallant et al.]. This favours superior overall response rates, as these patients usually suffer from less co-morbidities, drug-drug interactions (DDI), and other risks for treatment failure. The rate of patients with Acquired Immune Deficiency Syndrome (AIDS)-defining events enrolled in these trials was low.

Outside these trials, the number of patients considered as late presenters (CD4 cell count <350/µl) when diagnosed with Human Immunodeficiency Virus (HIV) remains high across Europe [Camoni et al., Montlahuc et al.]. According to a definition proposed in 2009, the term late presentation is used for persons presenting for care with a CD4 count <350 cells/mL or presenting with an AIDS-defining event, regardless of the CD4 cell count. Late presentation with advanced disease is restricted to persons presenting for care with a CD4 count <200 cells/mL or presenting with an AIDS-defining event, regardless of the CD4 cell count [Antinori et al.]. Patients with CD4 cell counts <200/µl and/or AIDS events at first diagnosis are frequent in clinical practice [Rafetti et al, Sobrino-Vegas et al, Late presenters working group in COHERE in EuroCoord et al.].

Strategic trials in this patient group thus far focused on time of treatment initiation to prevent immune reconstitution syndromes (IRIS) [Abdool Karim et al., Blanc et al.] or disease course of already diagnosed opportunistic infections (OIs) [Zolopa et al.; Manzardo C et al.]. The AIDS Clinical Trials Group (ACTG protocol 5164) reported that starting ART within the first 30 days after a diagnosis of non-tuberculosis (TB) OIs was associated with a lower rate of AIDS progression and death, compared to delaying initiation of ART, without an increase in adverse outcomes [Zolopa et al.].

Much less is known about which ART regimens perform best in late presenters in terms of viral efficacy, immune reconstitution, improvement of AIDS-related co-morbidities and adverse events (AEs). No specific combinations have been compared in sufficiently powered randomised clinical trials, and all regimens considered in international guidelines for first line therapies are judged as equal standard of care for these patients. Initially, protease inhibitor (PI) containing regimens were frequently used in patients presenting late or with AIDS defining events [Mussini et al.].

However, specifically regimens containing integrase inhibitors (INI) are promising candidates for treatment combinations in patients with CD4 cell counts <200/µl due to their antiviral activity and rapid decline of viral load, beneficial side-effect profile and metabolism pathways compared to other regimens. Also, integrase inhibitors such as dolutegravir (DTG) and bictegravir (BIC/B) have high genetic barriers, thereby preventing resistance mutation development and ensuring sufficient antiviral activity in case of preexisting mutations against nucleosides [Demarest et al.]. Therefore, in cases when ART needs to be initiated before genotypic testing results are available, current European AIDS Clinical Society (EACS) Guidelines (EACS Treatment Guidelines 9.0) recommend to include a drug with a high genetic barrier to resistance in the first-line regimen (e.g. PI or DTG). Whilst some reports describe a higher risk for IRIS in patients receiving integrase inhibitors [Wijting et al., Dutertre et al., Psichogiou et al.], a meta-analysis did not [Hill et al.]. We therefore propose a strategic clinical trial to compare an INI containing regimen versus a boosted PI regimen in patients with advanced HIV-infection.

1.1 Funding and Collaborators

Gilead Sciences, Inc. (Gilead) is the Funder for this Investigator-led study and will provide financial support, as well as supplying the study drug (Biktarvy®) for the INI containing treatment regimen.

Janssen Pharmaceutica NV (Janssen) will also be providing support for the study by supplying the study drug (Symtuza®) for the boosted PI treatment regimen, as well as funds for the associated study drug management costs.

1.2 Assessment and management of risk

1.2.1 B/F/TAF

Experience from Clinical Studies in Treatment-Naïve Patients

Assessment of adverse reactions (ARs) is based on pooled data from two 48-week controlled clinical studies (GS-US-380-1489 ("Study 1489") and GS-US-380-1490 ("Study 1490")) in which 1274 treatment-naïve patients received B/F/TAF (N=634), abacavir (ABC)/DTG/lamivudine (3TC) (N=315), or DTG+FTC/TAF (N=325).

The ARs are listed below by system organ class and frequency. Frequencies (based on all treatment-emergent AEs, regardless of relationship to study drug) are defined as follows: very common (≥10%), common (≥1% and <10%) or uncommon (≥0.1% and <1%).

NERVOUS SYSTEM DISORDERS

Very common: headache

GASTROINTESTINAL SYSTEM DISORDERS

Very common: diarrhoea

Common: nausea, vomiting, abdominal pain, dyspepsia, flatulence

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

Common: rash

Uncommon: Urticaria

GENERAL DISORDERS AND ADMINISTRATION SITE REACTIONS

Common: fatigue

Changes in Serum Creatinine: BIC has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 96. In Studies 1489 and 1490, median (Q1, Q3) serum creatinine increased by 0.10 (0.03, 0.17) mg/dL, 0.11 (0.03, 0.18) mg/dL, and 0.11 (0.04, 0.19) mg/dL from baseline to Week 96 in the B/F/TAF, ABC/DTG/3TC, and DTG+FTC/TAF groups, respectively. There were no discontinuations due to renal adverse events through Week 96 in B/F/TAF clinical studies.

Changes in Bilirubin: Total bilirubin increases were observed in 12% of patients administered B/F/TAF through Week 96. Increases were primarily Grade 1 (9%) and Grade 2 (3%) and were not associated with hepatic ARs or other liver related laboratory abnormalities. There were no discontinuations due to hepatic AEs through Week 96 in B/F/TAF clinical studies.

Clinical Experience

The efficacy and safety of B/F/TAF in HIV-1 infected, treatment-naïve adults are based on 48-week data from two randomised, double-blind, active-controlled studies, Study 1489 (N=629) and Study 1490 (N=645).

The efficacy and safety of B/F/TAF in virologically-suppressed HIV-1 infected adults are based on 48-week data from a randomised, double-blind, active-controlled study, GS-US-380-1844 ("Study 1844") (N=563); and a randomised, open-label, active-controlled study, GS-US-380-1878 ("Study 1878") (N=577).

The efficacy and safety of FTC+TAF (components of B/F/TAF) in HIV-1 infected, virologically-suppressed patients with mild to moderate renal impairment is based on 144-week data from an open-label study, GS-US-292-0112 ("Study 112") (N=242).

The efficacy and safety of FTC+TAF in adult patients coinfected with HIV-1 and chronic hepatitis B (HBV) are based on 48-week data from an open-label study, GS-US-292-1249 ("Study 1249") (N=72). The efficacy and safety of B/F/TAF in adult patients coinfected with HIV-1 and chronic HBV are also supported by 48-week data in 8 HIV/HBV coinfected adults treated with B/F/TAF in Study 1490 and 8 HIV/HBV coinfected adults treated with B/F/TAF in Study 1878.

Treatment-Naïve Patients

In Study 1489, patients were randomised in a 1:1 ratio to receive either B/F/TAF (N=314) or ABC/DTG/3TC (600/50/300 mg) (n=315) once daily. In Study 1490, patients were randomised in a 1:1 ratio to receive either B/F/TAF (N=320) or DTG+FTC/TAF (50+200/25 mg) (N=325) once daily.

In Studies 1489 and 1490, the mean age was 35 years (range 18-77), 89% were male, 58% were White, 33% were Black, and 3% were Asian. 24% of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL (range 1.3-6.6). The mean baseline CD4+ cell count was 460 cells/mm^3 (range 0-1636) and 11% had CD4+ cell counts less than 200 cells/mm^3. 18% of patients had baseline viral loads greater than 100,000 copies/mL. In both studies, patients were stratified by baseline HIV-1 RNA (≤100,000 copies/mL, >100,000 copies/mL to ≤400,000 copies/mL, or >400,000 copies/mL), by CD4 count (<50 cells/µL, 50-199 cells/µL, or ≥200 cells/µL), and by region (US or ex-US).

Treatment outcomes of Studies 1489 and 1490 through Week 48 are presented in Table 1-1.

Table 1-1 Pooled Virologic Outcomes of Studies 1489 and 1490 at Week 48 in Treatment-Naïve Patients[a]

	B/F/TAF (N=634)[b]		**ABC/DTG/3TC (N=315)[c]**	**DTG+FTC/TAF (N=325)[d]**
HIV-1 RNA < 50 copies/mL	91%	93%	93%	
Treatment Difference (95% CI) B/F/TAF vs Comparator	-	-2.1% (-5.9% to 1.6%)	-1.9% (-5.6% to 1.8%)	
HIV-1 RNA ≥ 50 copies/mL[e]	3%	3%	1%	
No Virologic Data at Week 48 Window	6%	4%	6%	
Discontinued Study Drug Due to AE or Death[f]	<1%	1%	1%	
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[g]	4%	3%	4%	
Missing Data During Window but on Study Drug	2%	<1%	1%	

[a] Week 48 window was between Day 295 and 378 (inclusive).
[b] Pooled from Study 1489 (N=314) and Study 1490 (N=320).
[c] Study 1489
[d] Study 1490
[e] Includes patients who had ≥ 50 copies/mL in the Week 48 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an AE, death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

[f] Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
[g] Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

B/F/TAF was non-inferior in achieving HIV-1 RNA < 50 copies/mL at Week 48 when compared to ABC/DTG/3TC and DTG+FTC/TAF, respectively. Treatment outcomes were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count.

In Studies 1489 and 1490, the mean increase from baseline in CD4+ count at Week 48 was 207, 229, and 201 cells/mm^3 in the pooled B/F/TAF, ABC/DTG/3TC, and DTG+FTC/TAF groups, respectively.

Bone Mineral Density: In Study 1489, bone mineral density (BMD) change from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry. In patients who had both baseline and Week 48 hip and lumbar spine BMD measurements (N=257 and 267 in the B/F/TAF group and N=270 and 274 in the ABC/DTG/3TC group, for hip and lumbar spine, respectively), mean percentage changes in BMD were similar in the B/F/TAF group compared to the ABC/DTG/3TC group for hip (-0.8% vs -1.0%) and lumbar spine (-0.8% vs -0.6%).

Pharmacology

Mechanism of Action:

BIC: BIC is an Integrase Strand Transfer Inhibitor (INSTI) that binds to the integrase active site and blocks the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

BIC has activity that is specific to HIV-1 and HIV-2.

FTC: FTC is a nucleoside analogue of 2'-deoxycytidine. FTC is phosphorylated by cellular enzymes to form FTC triphosphate. FTC triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase (RT), which results in DNA chain-termination.

FTC has activity that is specific to HIV-1 and HIV-2 and HBV.

FTC triphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there was no evidence of toxicity to mitochondria in vitro and in vivo.

TAF: TAF is a phosphonamidate prodrug of TFV (2'-deoxyadenosine monophosphate analogue). TAF is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than TDF in loading TFV into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macrophages. Intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite TFV diphosphate. TFV diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination.

TFV has activity that is specific to HIV-1 and HIV-2 and HBV. In vitro studies have shown that both FTC and TFV can be fully phosphorylated when combined in cells. TFV diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ and there is no evidence of mitochondrial toxicity in vitro based on several assays including mitochondrial DNA analyses.

Antiviral Activity:

B/F/TAF: The triple combination of B, F and TAF demonstrated synergistic antiviral activity in cell culture.

BIC: The antiviral activity of BIC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4+ T-lymphocytes. The

EC_{50} values for BIC were in the range of < 0.05 to 6.6 nM. The protein-adjusted EC_{95} of BIC was 361 nM for wild type HIV-1 virus.

BIC displayed antiviral activity in cell culture against HIV-1 groups (M, N, O), including subtypes A, B, C, D, E, F, and G (EC_{50} values ranged from < 0.05 and 1.71 nM), and activity against HIV-2 (EC_{50} = 1.1 nM).

In a study of BIC with representatives from the major classes of approved anti-HIV agents (nucleoside reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), INSTIs, and PIs), additive to synergistic antiviral effects were observed. No antagonism was observed for these combinations.

FTC: The antiviral activity of FTC against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI CCR5 cell line, and PBMCs. The EC_{50} values for FTC were in the range of 0.0013 to 0.64 µM.

FTC displayed antiviral activity in cell culture against HIV-1 clades A, B, C, D, E, F, and G (EC_{50} values ranged from 0.007 to 0.075 µM) and showed activity against HIV-2 (EC_{50} values ranged from 0.007 to 1.5 µM).

In two-drug combination studies of FTC with NRTIs, NNRTIs, PIs, and INSTIs, additive to synergistic effects were observed. No antagonism was observed for these combinations.

TAF: The antiviral activity of TAF against laboratory and clinical isolates of HIV-1 subtype B was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4 T lymphocytes. The EC_{50} values for TAF were in the range of 2.0 to 14.7 nM.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 and 12.0 nM), and activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM).

In a study of TAF with a broad panel of representatives from the major classes of approved anti-HIV agents (NRTIs, NNRTIs, INSTIs, and PIs), additive to synergistic antiviral effects were observed. No antagonism was observed for these combinations.

<u>Pharmacokinetic Properties</u>

Absorption:

BIC: BIC is absorbed following oral administration with peak plasma concentrations occurring at 2-4 hours after administration of B/F/TAF. Relative to fasting conditions, the administration of B/F/TAF with either a moderate fat (~600kcal, 27% fat) or high fat meal (~800kcal, 50% fat) resulted in an increase in BIC AUC (24%). This modest change is not considered clinically meaningful and B/F/TAF can be administered with or without food.

FTC: FTC is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1.5-2 hours after administration of B/F/TAF.

The mean absolute bioavailability of an FTC 200 mg capsule was 93%. The mean absolute bioavailability of the FTC 10 mg/mL oral solution was 75%.

FTC systemic exposure was unaffected when FTC was administered with food and B/F/TAF can be administered with or without food.

TAF: TAF is rapidly absorbed following oral administration with peak plasma concentrations occurring at 0.5-2 hours after administration of B/F/TAF.

Relative to fasting conditions, the administration of TAF with a moderate fat meal (~600kcal, 27% fat) and a high fat meal (~800kcal, 50% fat) resulted in an increase in AUC_{last} of 48% and 63% respectively.

These modest changes are not considered clinically meaningful and B/F/TAF can be administered with or without food.

B/F/TAF: The multiple dose PK parameters of the components of B/F/TAF are provided in Table 1-2.

Table 1-2 Multiple Dose PK Parameters of BIC, FTC, and TAF Following Oral Administration of B/F/TAF With or Without Food in HIV-Infected Adults.

Parameter Mean (%CV)	Bictegravir[a]	Emtricitabine[b]	Tenofovir Alafenamide[c]
C_{max} (microgram per mL)	6.15 (22.9)	2.13 (34.7)	0.121 (15.4)
AUC_{tau} (microgram·hour per mL)	102 (26.9)	12.3 (29.2)	0.142 (17.3)
C_{trough} (microgram per mL)	2.61 (35.2)	0.096 (37.4)	NA

CV = Coefficient of Variation; NA = Not Applicable

[a] From Population PK analysis in Studies 1489, 1490, 1844, and 1878; N = 1193

[b] From Intensive PK analysis in Studies 1489, 1490, 1844, and 1878; N = 77

[c] From Population PK analysis in Studies 1489 and 1490; N = 486

Please refer to the latest prescribing information for further information about clinical studies involving BIC.

1.2.2 Risk/Benefit Assessment for the Study

All patients with HIV-1 infection should receive effective ART. Potential risks associated with all classes of ARVs include IRIS. The risk of class effects is considered to be low. Important identified risks appropriately managed by study inclusion/exclusion criteria as well as through close clinical and laboratory monitoring during the study, are as follows: hypersensitivity reaction, including liver injury, and allergy to any components of the regimens. Interim data will also be reviewed by an independent data monitoring committee.

Potential benefits may include provision of a new ART that is not currently available, and which may have fewer side effects than alternative therapies. The benefits of participation for patients receiving B/F/TAF include provision of a therapy with less DDI due to the non-boosting regimen. Other potential benefits include provisions of fixed dose combination (FDC) therapy, and the knowledge that patient participation will contribute to the body of knowledge of HIV therapies.

Following a chronic 39-week study in monkeys, animals administered the highest dose of BIC (1000 mg/kg/day) had bile duct hyperplasia (increased cell growth) and hypertrophy (increased cell size), and some increased cell growth and inflammation in nearby liver cells. These effects were not seen in monkeys administered the mid-level dose (200 mg/kg/day), and these animals had plasma BIC exposures that were approximately 5-fold above human exposures when given the B/F/TAF FDC. No adverse drug reactions associated with liver or bile duct problems have been identified in humans treated with BIC.

Darunavir as a component of D/C/F/TAF fix-dose combination can cause transient and usually asymptomatic elevations in serum aminotransferase levels and has been linked to rare instances of clinically apparent, acute liver injury. No dose adjustment of D/C/F/TAF is required in patients with mild or moderate (Child-Pugh Class A/B) hepatic impairment or in patients with estimated glomerular filtration rate according to the Cockcroft-Gault formula (eGFRCG) ≥ 30 mL/min. The most frequent adverse reactions reported were diarrhea, nausea, fatigue, headache, and rash. Darunavir contains a sulphonamide moiety and should be used with caution in patients with a known sulphonamide allergy. Co-administration of D/C/F/TAF and medicinal products primarily metabolised by CYP3A may result in increased systemic exposure to such medicinal products, which could increase or prolong their therapeutic effect and adverse reactions.

The overall benefit-risk assessment for B/F/TAF and D/C/F/TAF is favourable at this time.

1.2.3 Rationale for Dose Selection

B/F/TAF

The B/F/TAF FDC containing B (50 mg), F (200 mg), and TAF (25 mg), has been approved by the Food and Drugs Administration (FDA) for use once daily for the treatment of HIV-1 infection in adults. This regimen has been submitted to the European Medicines Agency for approval and was approved in June 2018. Phase 3 clinical trials with the B/F/TAF FDC in treatment-naïve patients have shown it to be safe and well tolerated and have demonstrated non-inferiority to ABC/DTG/3TC and DTG + F/TAF at Week 48 by snapshot algorithm (GS-US-380-1489 and GS-US-380-1490). B/F/TAF contains 25 mg of TAF, the approved and recommended dosage for the treatment of HBV infection with other antiretrovirals (ARVs) for treatment of HIV/HBV co-infection (Please refer to the Biktarvy® SmPC for further information).

D/C/F/TAF

The D/C/F/TAF FDC (Symtuza®) containing D (800 mg), C (150 mg), F (200 mg), and TAF (10 mg), has been approved in the European Union (EU) for use once daily for the treatment of HIV-1 infection in adults.

2. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

2.1 Primary objective

- To demonstrate the non-inferiority of an INI containing regimen [bictegravir (B)/emtricitabine (F)/tenofovir alafenamide (TAF) QD] versus a boosted PI regimen [darunavir (D)/cobicistat (C)/ emtricitabine (F)/tenofovir alafenamide (TAF) QD] in patients with advanced HIV infection.

2.2 Secondary objectives

- To investigate the immunological and virological response, tolerability, resistance development, discontinuation of therapy due to tolerability, quality of life (QoL) and IRIS incidence.

2.3 Exploratory objectives

- To assess whether virological response is better predicted by deep sequencing rather than standard population sequencing.

2.4 Outcome measures/endpoints

2.4.1 Primary endpoint/outcome

- Time to failure, as the first occurrence of any of the following components:

1. Virological reasons

a) Insufficient virological response, either:
    a. HIV-1 RNA reduction < 1 log 10 copies/mL at week 12, or
    b. Viral load > 50 HIV-1 RNA copies/mL at week 48
b) Viral rebound, which is subsequently confirmed at the following scheduled or unscheduled visit, defined as either:
    a. Rebound of HIV-1 RNA to >200 copies/mL after having achieved HIV-1 RNA <50 copies/mL
    b. Rebound of HIV RNA by >1 log 10 copies/mL from nadir value, for patients whose viral load has never been suppressed below 50 copies/mL

2. Clinical reasons*
    a) Death related to HIV, AIDS, OI/severe BI or complications of therapy including IRIS
    b) Any new or recurrent AIDS defining event on, or after 28 days of therapy
    c) Any new serious non-AIDS defining event documented by the endpoint review committee (including severe BI, end stage liver disease, renal failure, cardiovascular event, and non-AIDS related malignant disease)
    d) Clinically relevant AEs of any grade or IRIS which require treatment interruption (lasting > 5 days) of INI or boosted PI therapy within the first 48 weeks after randomisation
    Note: Discontinuation of BIC or boosted DRV followed by (within 5 days) continuation with another INI or PI, respectively, is not considered as a strategy failure or endpoint.

2.4.2 Secondary endpoints/outcomes

- Proportion of patients with HIV-RNA viral load < 50 copies/mL at week 24, 36, 48
- HIV-1 drug resistance at confirmed virological failure (genotype)
- Time to reach CD4 count > 200/µL (first measurement)
- Proportion of patients with CD4 cell count < 200 µL and < 350µL at week 4, 8, 12, 24, 36, 48
- CD4/CD8 ratio at week 4, 8, 12, 24, 36, 48
- Incidence of IRIS in the two arms through week 48
- Incidence and duration of hospitalisation, rate of relapse of specific OI/BI through week 48
- Safety and tolerability, measured by Grade 2, 3 and 4 signs and symptoms and laboratory toxicities through week 48
- ART and OI/BI treatment changes and dose modifications due to toxicities and DDI with ART, and IRIS through week 48
- Health care resource use, including total inpatient days and emergency room visits through week 48
- QOL and functional status outcomes, including overall self-reported QOL and functional status compared in the two groups at week 48
- Discontinuation or modification of study medication due to insufficient virological response, resistance mutations at baseline, or resistance mutation development before week 48

2.4.3 Exploratory endpoints/outcomes

- Mutations detected by deep sequencing compared with those detected by population sequencing
- Proportion of patients with HIV-RNA viral load < 50 copies/mL at week 4, 8, 12

* Refer to Appendices 3 (AIDS-Defining Conditions), 4 (INSIGHT Serious Non-AIDS Events Criteria), 5 (INSIGHT Progression of HIV Disease Criteria) and 6 (Immune Reconstitution Inflammatory Syndrome Generic Criteria).

3 TRIAL DESIGN

An open-label, randomised, two arm, multicentre trial over 48 weeks to compare two strategies for HIV-1 infected patients with advanced disease, stratified according to country and baseline CD4 cell count (<50 cells/µL, 50-199 cells/µL, or ≥200 cells/µL).

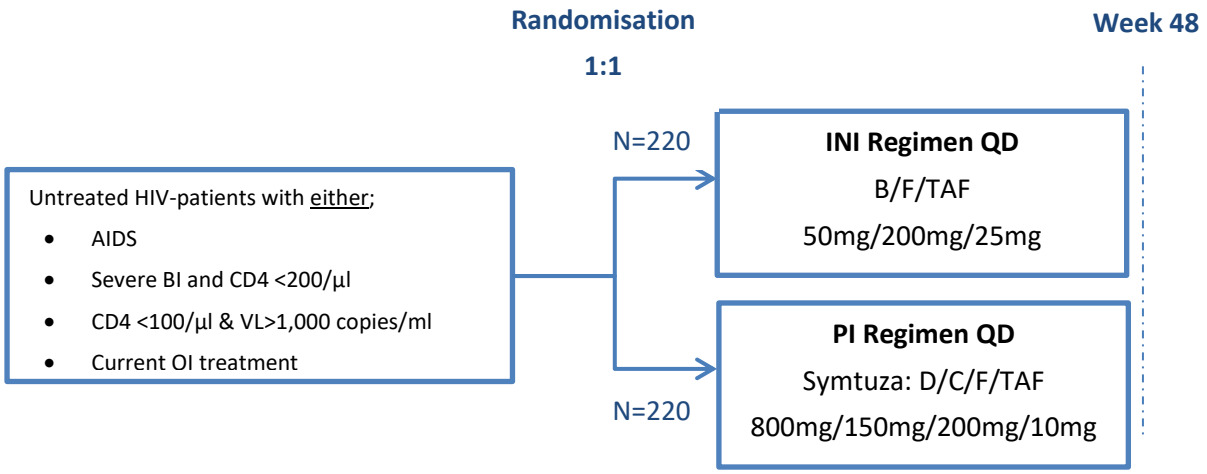
Patients will be randomised to receive either an integrated inhibitor containing regimen (B (50mg)/F (200mg)/TAF (25mg) [1 pill administered orally once daily for 48 weeks]) or a boosted PI regimen (D (800mg)/C (150mg)/F(200mg)/TAF (10mg) [1 pill administered orally once daily for 48 weeks]).

Study visits will take place at screening, baseline, weeks 4, 8, 12, 24, 36 and 48, as well as a follow-up visit 30 days following the week 48 visit.

Routine investigations will include HIV-1 RNA, CD4, CD8, haematology (including haemoglobin, white cell count and differential, platelets), biochemistry (including sodium, potassium, creatinine, phosphorus, albumin, glucose, alanine transaminase (ALT), aspartate aminotransferase (AST), ALP, total and indirect bilirubin, total cholesterol, HDL, LDL, triglycerides), QoL questionnaire (EuroQoL EQ-5D-3L), HIV Symptom Index (HIV-SI/SDM) urine sample (for haematuria, proteinuria, glycosuria, leukocytes, nitrites, pregnancy test in women of child-bearing potential (WOCBP)).

For a full list of investigations please see the table of assessments in Appendix 1.

3.1 Study Schema



4 STUDY SETTING

This study will be conducted within the NEAT ID network and include sites that have an excellent track record in clinical research and operate in up to eight countries. A full feasibility and qualification assessment plan will be undertaken for all potential sites. The sponsor will ensure that onsite visits are performed to assess GCP compliance, including (but not limited to); protocol adherence, informed consent documentation, data quality, drug accountability and overall site performance.

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria

Patients must meet all the following inclusion criteria to be eligible for participation into this study.

1. The ability to understand and sign a written informed consent form (ICF) and must be willing to comply with all study requirements.

2. Male or non-pregnant, non-lactating females[†].

3. Age ≥ 18 years.

4. Have documented, untreated HIV-1 infection with either:

   a) AIDS with any CD4 cell count (AIDS-defining conditions are listed within Appendix 3).

   Or

   b) Severe bacterial infection (BI)[‡] and must have a CD4 cell count < 200/µl within 28 days prior to study entry[§].

   Or

   c) Any symptoms or no symptoms and must have a CD4 cell count < 100/µL within 28 days prior to study entry and must have an entry HIV viral load > 1000 copies/mL.

   Or

   d) Currently receiving treatment for OI[**].
      i. Subjects with other serious OIs, including other AIDS-defining and AIDS-related OIs for which appropriate therapy other than ART exists are eligible, but Investigator approval must be obtained.
      ii. Current OI treatment can have been discontinued prior to start of ART.

5. Have an entry HIV viral load > 1000 copies/mL
6. Have the ability to take oral medications.

[†] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade haemoglobin based on the gender with which they identify (i.e. a transgender female should be graded using the female sex at birth haemoglobin laboratory values)

[‡] A severe BI consists of any of bacterial pneumonia, IBI or any bacterial infectious disorder with grade 3 severity (severe or medically significant but not immediately life-threatening, see Appendix 2) or requiring unscheduled hospital admission. An IBI is defined as the isolation of a bacterial organism from a normally sterile body site, or for bacterial nucleic acid to be detected at a normally sterile body site. Sterile body sites include blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, joint fluid, bone aspirate, or a deep tissue abscess.

[§] Study entry is defined as the start of the screening process

[**] Including Pneumocystis jrovecii pneumonia [PCP]; disseminated histoplasmosis; cytomegalovirus [CMV] infection; toxoplasmic encephalitis; other atypical non-tuberculous, non-MAC mycobacterial infections; or other serious, invasive bacterial infections (IBI).

7. Females of childbearing potential and heterosexually active males must be willing to use a highly effective method of contraception and be willing to continue practising these birth control methods during the trial and for at least 30 days after the last dose of study medication. See Appendix 7 for further details.
   Such methods include:
   - True abstinence from penile-vaginal intercourse, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception).
   - Non-hormonal Intrauterine device or non-hormonal intrauterine system that meets the effectiveness criteria as stated in the product label.
   - Male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject.
   - Combined (oestrogen and progesterone containing) hormonal contraception associated with the inhibition of ovulation*:
     - Oral
     - Intravaginal
     - Transdermal
   - Bilateral tubal occlusion

- Note: Non-childbearing potential is defined as either post-menopausal (had amenorrhea for at least 12 months and have an FSH (follicle stimulating hormone) of greater than 40 IU/L or, if FSH testing is not available, they have had amenorrhea for 24 consecutive months) or physically incapable of becoming pregnant with documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy).

*If a patient is randomised to Symtuza, an alternative highly effective method of contraception should be used

5.2 Exclusion criteria

1. Any therapeutic ARV which commenced less than 2 weeks prior to screening and which was taken for more than 48 hours.

2. Systemic cancer chemotherapy within 30 days prior to study entry, or current treatment for cancer (with the exception of Kaposi's sarcoma) or lymphoma.

3. Current or anticipated use of contraindicated medications (see current Summary of Product Characteristics (SmPC) for Symtuza® and Biktarvy®) or anticipated systemic chemotherapy during study enrolment (administration of any contraindicated medication must be discontinued prior to the baseline visit and for the duration of the study).

4. Known resistance to the components of study medications (see section 6.1.3 for more details).

5. History or symptoms of advanced renal and/or hepatic impairment. Such as, kidney failure requiring dialysis; eGFR <30 mL/min; hepatic transaminases (AST and ALT) > 5 x upper limit of normal (ULN); or, platelet count <50,000.

6. Current drug or alcohol use that, in the opinion of the Investigator, would cause interference with the study.

7. Cryptococcal meningitis or active TB or current or expected treatment requiring Rifampicin or Rifabutin (patients with expected latent TB may have a TB test (IGRAs e.g. ELISPOT, QuantiFERON etc.) at their screening visit).

8. History or presence of allergy to the study drugs or their components, or drugs of their class.

9. Using any concomitant therapy disallowed as per the product labelling for the study drugs.

10. Any investigational drug within 30 days prior to the study drug administration.

11. Patients with severe (Child Pugh class C) hepatic impairment.

12. Women who are pregnant, breastfeeding or plan to become pregnant or breastfeed during the study.

6 TRIAL PROCEDURES

The schedule of assessments is summarised in Appendix 1.

Please note that if additional tests/procedures are required in accordance with local practice, then these should still be performed (no usual tests/procedures should be withheld from the patients during the study).

6.1 Recruitment

Following full written informed consent, sites must keep a record of all screening and enrolled participants using screening and enrolment logs. Diagnostic tests procedures may be used in determining eligibility however, written informed consent must be obtained prior to any study specific procedures. All information collected for eligible participants will be pseudo-anonymised and recorded in the Investigator Site File (ISF).

All eligible consented participants will be given a unique study identifier via an electronic study database.

Anonymised information that will be collected:

- age
- gender
- ethnicity
- whether the patient is enrolled or not enrolled
- if the patient is deemed ineligible, then the reason for this; or if they are eligible but choose not to participate, then their reason for declining (where available)

6.1.1 Patient identification

Patients will be identified through clinic visits by their direct study medical care team and visits will be captured on a participant screening log. Additionally, Investigators may use advertisements; however, these must be approved by the Independent Ethics Committee/Institutional Review Board (IEC/IRB) prior to use.

6.1.2 Screening

Written informed consent must be obtained from the subject prior to performing any study related evaluations or procedures.

Subjects will be provided with written information about the study in the form of a subject information sheet and will be allowed adequate time for questions and to consider the study before agreeing to participate. It will be the responsibility of the Investigator or co-investigator to obtain written informed consent prior to undertaking any procedures detailed in the protocol. This responsibility may be delegated to other suitably trained personnel if allowed according to country-specific regulations and approved by the local IEC.

The Investigator or designee must provide adequate explanation of the aims, methods, objectives and potential hazards of the study. It must also be explained to the subject that they are free to refuse or withdraw from the study for any reason without detriment to their future care or treatment.

See Appendix 1 for details of screening assessments required.

6.1.3 Resistance Testing and Results

Resistance test results obtained at screening may influence randomisation.

If resistance data of the RT, protease (Table 1 and 2), or integrase gene as described below become available after screening but before randomisation patients should not be randomised (and will be seen to be screen failures).

If data becomes available after randomisation, patients may be considered to switch to the other treatment arm at the investigator's discretion in the following scenarios:

1. Patients randomised to the DRV arm may be considered to switch to the BIC arm only if they have any of the resistance mutation patterns as described in Table 1. In these patients, only TAF and FTC would have full ARV activity. The decision should be made by the investigator after consultations with the LAPTOP study team.

Table 1: Resistance mutation patterns leading to intermediate of high-level resistance against DRV.

Resistance	**Mutation pattern[21]**											
Darunavir	V32I	L33F	K43T	M46I	I47V	I54L/M	G73T/S	L76V	V82A	I84V	L89V	L90M
Intermediate						L						+
Intermediate		+				L	T			+		+
Intermediate				+				+		+		
High	+		+	+	+	M			+			+
High	+	+		+	+	M			+			+
High	+					M	S			+	+	+

2. Patients randomised to the DRV or BIC arm may be considered to remain in their treatment arm or to switch to an alternative regime (e.g. PI + INI) only if they have any of the resistance mutation pattern as described in Table 2. Table 2 describes RT inhibitor associated resistance mutation pattern, in which intermediate or high-level resistance against FTC and TFV has to be expected. In these situations, only DRV or BIC would have full ARV activity. The decision to

remain on therapy or to switch should be made by the investigator after consultations with the LAPTOP study team.

Table 2: Resistance mutation patterns leading to intermediate of high-level resistance against FTC or tenofovir disoproxil fumarate (TDF).

Resistance		**Mutation pattern**									
FTC	***TDF***	M41L	E44D	K65R	D67N	T69D	K70R	M184V/I	L210W	T215Y	K219N/Q
High	Interm	+						V	+	+	
High	Interm				+		+	V		+	Q
High	Interm	+			+			V	+	+	
High	Interm			+				V			
High	Interm			+				I			
High	High	+	+		+				+	+	
High	High	+	+		+	+		V	+	+	
High	High	+	+		+			V	+	+	N

If any primary integrase strand transfer inhibitor resistance mutation (T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K) is identified please consult the LAPTOP study team. Resistance mutation patterns leading to possible resistance against BIC are Q148H/R/K plus 2 or more of the following mutations: (G140A/C/S, T97A, L74M, or E138A/K).

6.1.4 Consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to perform their role according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are outside standard routine care at the participating site. The right of a participant to refuse participation without giving reasons must be respected.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

6.1.5 The randomisation scheme

Patients will be randomly allocated (1:1) to receive a BIC containing regimen or boosted PI containing regimen for 48 weeks. Randomisation will be computer-generated in permuted blocks and stratified by country and baseline CD4 cell count (<50 cells/µL, 50-199 cells/µL, or ≥200 cells/µL). Randomisation will be done at the baseline visit (date of the study treatment initiation). This study is open-label, therefore, all investigators, site pharmacists, study nurses and subjects will be unmasked and aware of the treatment allocation throughout the study.

6.1.6 Method of implementing the allocation sequence

The method will be detailed in the randomisation plan.

6.2 Baseline data

See Appendix 1 for details of assessments required.

6.3 Treatment Phase Assessments

See Appendix 1 for details of assessments required.

6.4 Follow-Up/Early Termination Visit (ETV)

In the case of early termination, every attempt will be made to ensure the subject has a termination visit. Patients will be encouraged to attend for remaining visits and complete study assessments to week 48 even if they are no longer taking study medication.

See Appendix 1 for details of assessments required.

6.5 Withdrawal criteria

A subject is free to withdraw from the study at any time. In addition, the Investigator may decide, for reasons of medical prudence, to stop study medication (e.g. lack of efficacy).

All patients who discontinue study medication will be followed up and encouraged to attend for study visits up until week 48.

If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study and the reason for withdrawal recorded in the Case Report Form (CRF).

Study medication may also be discontinued in the following instances:

1. If the subject withdraws their consent.
2. If the investigator considers in the interest of the subject (i.e. intercurrent illness, unacceptable toxicity) that it is best for them to stop study medication.
3. The subject fails to comply with the protocol requirements or fails to cooperate with investigator.
4. Pregnancy during the study (for patients receiving B/F/TAF, the study medication must be discontinued).
5. Discontinuation of the study at the request of the Sponsor, regulatory agency, or an IRB/IEC.

The date and reasons for stopping medication will be clearly stated on the subject's CRF and source document. Every attempt should be made to arrange follow up visits for subjects who are withdrawn from study medication. This visit should involve assessments as outlined in Appendix 1.

Subjects withdrawing from the trial should be offered alternative treatment as per the local standard of care by the Investigator.

Additional subjects may be recruited to account for any withdrawals should this be deemed necessary by the statistician or CI.

6.6 Storage and analysis of samples

All samples (with the exception of centrally analysed resistance samples) will be analysed at each site's local laboratory. After analysis the samples will be destroyed in accordance with local laboratory requirements. Throughout the study a total of 234ml of blood will be collected from each patient, this equates to 26ml per visit.

Collection, processing and storage instructions will be detailed in a separate laboratory manual.

6.6.1 Resistance testing

Next generation sequencing (deep sequencing) may be performed centrally to evaluate the significance of the HIV-1 mutations detected by this method, which are identified during standard population sequencing of the HIV viral load response.

Blood samples for these tests will be taken at the baseline visit and treatment phase visits (Week 4, 8, 12, 24, 36 and 48). A sample will be taken at the ETV for patients with virological failure identified outside of a scheduled visit.

Samples will be shipped on a periodic basis from the sites to ACM Global for central storage and shipped to Monogram Biosciences for analysis.

At the end of the study, samples taken from patients that do not have virological failure will be destroyed, either locally, or at ACM Global.

Collection, processing and storage instructions will be detailed in a separate laboratory manual.

See Appendix 1 for details of assessments required.

6.7 Virological Failure

Virological failure is defined as:

Insufficient virological response, either:

- HIV-1 RNA reduction < 1 log 10 copies/mL at week 12, or
- Viral load > 50 HIV-1 RNA copies/mL at week 48

Or viral rebound, which is subsequently confirmed at the following scheduled or unscheduled visit, defined as either:

- Rebound of HIV-1 RNA to >200 copies/mL after having achieved HIV-1 RNA <50 copies/mL
- Rebound of HIV RNA by >1 log 10 copies/mL from nadir value, for patients whose viral load has never been suppressed below 50 copies/mL

Local resistance testing should also be carried out in the event of viral failure from the first sample and patients should discontinue study medication and receive rescue medication at investigators discretion.

6.8 End of trial

The end of the trial is defined as the date of the last visit of the last subject undergoing the trial in any country.

The sponsor must notify the Competent Authority (CA) and main IRB/IEC of the end of a clinical trial within 90 days of its completion.

7 TRIAL MEDICATION

Name and description of investigational medicinal product(s)

At baseline, participants will be enrolled into one of two treatment arms, either a BIC-based regimen or a DRV-based regimen:

INI containing regimen (BIC-based regimen): One combined B 50mg/F 200mg/TAF 25mg tablet taken orally once daily for up to 48 weeks without regard to food.

Boosted PI regimen (DRV-based regimen): One combined D 800mg/C 150mg/F 200mg/TAF 10mg tablet taken orally once daily for up to 48 weeks with the addition of food.

Participants will take the study medication from baseline, as randomised, to week 48.

Please refer to the study specific pharmacy manual for more information.

7.1 Summary of Product Characteristics (SmPC), and Reference Safety Information (RSI)

Information about Emtricitabine (Emtriva®, F/FTC)

Emtricitabine (5-fluoro-1-[(2R, 5S)-2-(hydroxymethyl)-[1, 3]-oxathiolan-5-yl] cytosine, FTC) is a NRTI that has demonstrated potent and selective inhibition of the HIV. In HIV-infected adults, FTC is administered as a 200mg QD dose concurrently with other ARV drugs. The 200mg FTC capsule formulation was approved by the United States (US) FDA for marketing on 2 July 2003 and is available under the name Emtriva®. In the European Union (EU), marketing authorisation was granted for both the 200mg Emtriva® capsule formulation and a 10mg/mL Emtriva® oral solution formulation on 24 October 2003, with indications for the treatment of HIV infection concurrently with other ARV drugs in both adult and pediatric patients.

Further information is available in the current Prescribing Information for Emtriva®.

Information about Tenofovir alafenamide (TAF, GS-7340)

Tenofovir alafenamide (GS-7340, TAF) is a second-generation oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. TFV is metabolised intracellularly to the active metabolite, tenofovir diphosphate, a competitive inhibitor of HIV-1 RT that terminates the elongation of the viral DNA chain. The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV.

Further information about the co-formulated version of TAF/FTC is available in the current Prescribing Information for Descovy®.

Information about Darunavir (Prezista ®, D/DRV)

Prezista® is a PI which demonstrated potent inhibition of the HIV. DRV received marketing authorisation valid throughout the EU 12/02/2007. Co-administered with low dose ritonavir is indicated in combination with other ARV medicinal products for the treatment of HIV-1 infection in adult and paediatric patients from the age of 3 years and at least 15 kg body weight. Co-administered with cobicistat (C) is indicated in combination with other ARV medicinal products for the treatment of HIV-1 infection in adult patients. In ART-naïve adult patients the recommended dose regimen is 800 mg once daily with C 150 mg once daily or ritonavir 100 mg once daily taken with food.

Further information about DRV is available in the current Prescribing Information for Prezista®.

Information about Darunavir/Cobicistat/Emtricitabine/Tenofovir alafenamide (D/C/F/TAF) fixed dose combination (Symtuza®)

Symtuza® is a boosted PI indicated for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg). Symtuza® received marketing authorisation valid throughout the EU in September 2017. The recommended dose regimen in adults and adolescents aged 12 years and older, weighing at least 40 kg, is one tablet taken once daily with food. Each film coated tablet contains 800 mg of D (as ethanolate), 150 mg of C, 200 mg of F, and 10 mg of TAF.

Further information about the D/C/F/TAF FDC is available in the current Prescribing Information for Symtuza®.

The Reference Safety Information for this regimen will be the formally approved and implemented version of the Summary of Product Characteristics for Symtuza® provided to investigators by the sponsor.

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Bictegravir (BIC)

BIC is an inhibitor of HIV-1 integrase that is being evaluated for the treatment of HIV-1 infection. Antiviral testing has shown that BIC is active against a broad panel of HIV-1 viral lab strains and clinical isolates. BIC is fully active against a panel of mutant viruses with resistance to NRTIs, NNRTIs, and PIs. Integrase mutant viruses that are resistant to the INSTIs raltegravir (RAL) and elvitegravir (EVG) remain largely sensitive to BIC. Gilead Sciences (Gilead) has co-formulated BIC with the NRTI F and TAF into an FDC tablet that is suitable for once-daily use.

Further information about the B/F/TAF fix-dose tablet is available in the current Prescribing Information for Biktarvy®.

The Reference Safety Information for this regimen will be the formally approved and implemented version of the Summary of Product Characteristics for Biktarvy provided to investigators by the sponsor.

7.2 Drug storage and supply

Investigators are to ensure that the investigational medicinal product (IMP) is only used in accordance with the protocol. Drug supplies will be kept in a secure, limited access storage area under the recommended storage conditions, and accessible only to those authorised by the investigator to dispense to eligible subjects.

The investigator will ensure that records are maintained showing the receipt and dispensation for all study supplies. A drug accountability log will be kept with the investigational supplies for reconciliation purposes. This should be used to record the identification of the subject to whom the IMP was dispensed, the date and quantity dispensed, and the quantity unused/returned by the subject. This will be verified by the study monitor.

Partially used or empty containers may be destroyed by the pharmacy/designee at local site only after the study monitor has completed drug accountability. The pharmacy/designee are required to document destruction for verification by the sponsor.

Further information can be found in the pharmacy manual.

7.3 Preparation and labelling of Investigational Medicinal Product

Both the INI containing regimen (B/F/TAF) and the boosted PI regimen (D/C/F/TAF) tablets will be labelled with Annex 13 compliant labels and QP certified by PCI Pharma Services; who will supply directly to each site on request of the sponsor.

Further information can be found in the pharmacy manual.

7.4 Dosage schedules

Patients will be randomised into one of two treatment arms.

INI containing regimen (BIC-based regimen): One combined B 50mg/F 200mg/TAF 25mg tablet taken orally once daily for up to 48 weeks without regard to food.

Boosted PI regimen (DRV-based regimen): One combined D 800mg/C 150mg/F 200mg/TAF 10mg tablet to be taken orally once daily for up to 48 weeks with the addition of food.

7.5 Dosage modifications

Please refer to section 6.5 for withdrawal and stopping rules.

Treatment modification will be captured as a secondary endpoint only and modifications will be based on the treating physician's judgement.

7.6 Known drug reactions and interaction with other therapies

See section 8.2 and RSI.

Drugs that affect the study medication and that are affected by the use of the study medication accordingly must be reviewed by the Investigator and/or avoided.

7.7 Concomitant medication

For a full list of contraindicated medications, please refer to the current the current Prescribing Information for for both Biktarvy® and Symtuza®

Prophylaxis for specific OI or TB shall be performed as per standard of care. Reference can be made to the EACS guidelines.

7.8 Trial restrictions

Please refer to inclusion and exclusion criteria listed in sections 5.1 and 5.2.

7.9 Assessment of adherence

Adherence during the trial will be monitored by subject questioning regarding missed tablets at each visit. The outcome of this questioning should be documented in the patient notes. Issues of adherence should be reported to the study monitor.

All subjects should return unused medication and containers at weeks 12, 24, 36 and 48 for pharmacy accountability purposes (see section 7.2).

7.10 Provision of treatment after the end of the trial

No post trial medication will be provided to patients. Following their last treatment visit at Week 48 patients will receive treatment as per local standard of care.

8 PHARMACOVIGILANCE

8.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as ARs.
Serious Adverse Event (SAE)	An SAE is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An AE that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	• A SAR, the nature and severity of which is not consistent with the information about the medicinal product set out in section 4.8 "***Undesirable Effect***" of the SmPC

"Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

8.2 Operational definitions for (S)AEs

AEs observed by the Investigator, or reported by the subject, and any remedial action taken, will be recorded in the subject's CRF and should be verifiable in the subject's notes throughout the study. The nature of each event, time of onset after drug administration, duration and severity will be documented together with the Investigator's opinion of the causal relationship to the investigational product (unrelated, unlikely, possible, probable, and definite).

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed.

Procedures such as surgery should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy noted on the CRF.

Planned procedures such as surgery scheduled prior to the subject's enrolment into the study do not need to be reported as AEs if these are documented as planned at the screening visit.

Clinically significant changes in physical examination and blood safety profiles should also be recorded as AEs.

8.2.1 Assessment of intensity

Severity should be recorded and graded according to the ACTG Grading Scale (Appendix 2).

Note: There is a distinction between the seriousness and the intensity of an AE. Severe is a measure of intensity; thus, a severe reaction is not necessarily an SAE. For example, a headache may be severe in intensity but would not be classified as serious unless it meets one of the seriousness criteria for serious events.

All events deemed to be Grade 4 (potentially life threatening) according to the ACTG grading scale should be routinely reported as an SAE. However, there may be occasions where in the investigator's clinical judgement they do not consider the event to be life threatening therefore they do not consider the event to meet the definition of an SAE. In these cases, the investigator must document clearly in the participants source documentation that the Grade 4 event has been assessed and why in their clinical judgement they do not consider the event to be life threatening.

8.2.2 Assessment of causality

The relationship to study drug of each AE will be assessed by the PI (or a delegated clinician) using the following definitions:

DEFINITE: distinct temporal relationship with drug treatment. Known reaction to agent or chemical group or predicted by known pharmacology. Event cannot be explained by subject's clinical state or other factors.

PROBABLE: reasonable temporal relationship with drug treatment. Likely to be known reaction to agent or chemical group or predicted by known pharmacology. Event cannot easily be explained by subject's clinical state or other factors.

POSSIBLE: reasonable temporal relationship with drug treatment. Event could be explained by subject's clinical state or other factors.

UNLIKELY: poor temporal relationship with drug treatment. Event easily explained by subject's clinical state or other factors.

UNRELATED: the event occurs prior to dosing. Event or intercurrent illness is due wholly to factors other than drug treatment.

8.2.3 Collection and Follow up of Adverse Events

All AEs, however minor, will be documented in the CRF whether or not the Investigator considers the event to be treatment related.

The AE reporting period will be from consent until the subject's final study visit. In addition, any untoward event that may occur subsequent to the reporting period that the Investigator assesses as possibly, probably or definitely related to the study drug medication should also be reported as an AE.

AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit.

All AEs should be followed up until they are resolved or the subject's participation in the study ends (i.e. until the final CRF is completed for that subject). In addition, all serious and non-serious AEs assessed by the Investigator as possibly related to the investigational medication should continue to be followed up to last subject visit. Such events should be followed until resolution, until no further change can reasonably be expected, or until 30 days following last subject visit.

8.2.4 Recording and Reporting of SAEs and SUSARs

Definition of an SAE can be found in section 8.1.

The SAE should be reported to the sponsor using the study specific Safety Event Reporting Form (SERF), within 24 hours of a member of the study team becoming aware of the event via e-mail to **Safety@rokcservices.com** or via the fax number provided on the SERF.

All SAEs occurring from the time of written informed consent until 30 days post cessation of trial treatment must be recorded on the study specific SAE Form and sent to the sponsor within 24 hours of the research staff becoming aware of the event.

For each SAE the following information will be collected in the SERF:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the Investigator
- details of the reporter(s)

Any change of condition or other follow-up information should be sent to the sponsor in a follow up SERF as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

The Sponsor representative (CI) will assess whether events suspected to be related to IMP-treatment would be considered expected or unexpected (using the formally approved and implemented version of the reference safety information (RSI) for either Symtuza® or Biktarvy®).

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and assessed by the CI as unexpected will be classified as SUSARs. The sponsor will inform the CA, the IRB/IEC and the funder as appropriate of SUSARs within the required expedited reporting timescales. The sponsor will update the Eudravigilance database, as required.

8.3 Responsibilities

8.3.1 **Principal Investigator (PI):**

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, and assessing causality (using the formally approved and implemented version of the reference safety information (RSI) for either Symtuza® or Biktarvy® provided to investigators by the sponsor).

2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
3. Ensuring that SAEs and SARs (including SUSARs) are followed up with the Sponsor if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

8.3.2 **Chief Investigator (CI) / delegate or independent clinical reviewer:**

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in reviewing seriousness and causality of SAEs reported, when required.
3. Using medical judgement in assignment of expectedness for all SARs reported (using the formally approved and implemented version of the reference safety information (RSI) for either Symtuza® or Biktarvy®)
4. Review of specific SAEs and SARs in accordance with the trial risk assessment, protocol and as detailed in the Trial Risk Based Monitoring Plan, and pharmacovigilance management plan (PVMP).
5. Ensure immediate review of all SUSARs.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs as needed.
7. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

8.3.3 **Sponsor:**

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Risk Based Monitoring Plan, and pharmacovigilance management plan (PVMP).
3. Reporting safety information to the independent oversight committees identified for the trial (Data Safety Monitoring Board (DSMB)/Trial Steering Committee (TSC)) according to the Trial Risk Based Monitoring Plan and committee charter documents.
4. Expedited reporting of SUSARs to the CA and IRB/IEC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for (at least annually) and notifying PIs of updates to the RSI for the trial.
7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the CA and IRB/IEC.

8.3.4 Data Safety Monitoring Board (DSMB):

In accordance with the DSMB Charter, periodically reviewing overall unblinded safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

8.3.5 Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DSMB regarding safety issues.

8.3.6 Endpoint Review Committee

The endpoint review committee will convene to review unblinded endpoint data, as and when required by the DSMB or TSC.

8.4 Notification of deaths

Any SAE, SAR or unexpected SAR that results in death should be immediately reported to the sponsor, refer to section 8.3 for SAE reporting format and timelines.

Deaths occurring more than 30 days after the final dose, which are considered to be unrelated to the study medication, should not be reported as an SAE.

8.5 Pregnancy reporting

Pregnancy information for all female participants who become pregnant while participating in the study will be collected on the study specific Pregnancy Reporting Form and should be reported to the Sponsor via e-mail to **Safety@rokcservices.com** or via the fax number provided on the SERF within 24 hours of becoming aware of the pregnancy or the pregnancy outcome. The participant will also be followed up to determine the outcome of the pregnancy, which will also be reported to the sponsor.

In the event of pregnancy, the participant may be withdrawn from the study (see Section 6.5).

Pregnancies in female partners of male participants should be reported as a special reporting situation (see Section 8.9).

8.6 Overdose

All participants should be counselled about the importance of taking the medications as prescribed and they should understand the quantity of medicine they should be taking. Participants must be told to contact their clinic immediately if they take too much medication. If the overdose fits the criteria of an SAE (see Section 8.1) it should be reported appropriately.

8.7 Reporting urgent safety measures

It is the responsibility of the investigator to apply the appropriate level of Urgent Safety Measure (USM) for the safety and protection of each participant in this study in order to prevent harm. USMs may be applied immediately without prior approval from the sponsor, CA or IRB/IEC. However, they must be reported to the sponsor and to the CI immediately (within 24 hours) who will then inform the CA and IRB/IEC according to local regulation.

8.8 Development Safety Update Reports

The sponsor will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the CA and IRB/IEC. The sponsor intends to submit a single safety report on all investigational medicinal products used in the clinical trial in accordance with Article 43(2) of the Clinical Trial Regulation (EU) No 536/2014.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

8.9 Special Reporting Situations

Special reporting situations should be reported to the sponsor via email to **Safety@rokcservices.com** within 24 hours of the research staff becoming aware of the event (as for SAEs).

The special situations include:

- Pregnancy exposure (maternal and paternal), breastfeeding and AEs in infants following exposure from breastfeeding
- Overdose (other than as defined in section 8.7), suspected abuse/misuse of the study product, and dependence
- Medication error
- DDI
- Inadvertent or accidental exposure to the study product (including occupational exposure)
- Any failure of expected of pharmacological or medical device action (i.e. lack of effect) of study product
- Unexpected therapeutic or clinical benefit from use of the study product
- Suspected transmission of an infectious agent via the study product
- Expired drug use and falsified medicine
- Off-label use of study product

Product Quality Complaint (PQC): Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study product after it is released for distribution. A complaint is any indication of the failure of the product to meet consumer or user expectations for quality or to meet performance specifications. It may allege an AR, injury, or malfunction associated with the use of the product. It may also involve the design, literature, packaging, advertising, availability, physical appearance, or promotion of a product.

9 STATISTICS AND DATA ANALYSIS

9.1 Sample size calculation

In the ANRS 146 OPTIMAL trial [Levy et al.], of late presenters, the proportion of patients with severe morbidity (new adverse drug event (ADE), other HIV related diseases, serious non-AIDS events, IRIS and death) was estimated at 12.2% per year in the boosted PI arm. The virological failure was estimated at 20% at week 48 in the DRV/r group of the IMEA 040 DATA study (Slama L et al) that recruited a similar population. As a few subjects will meet more than one of these criteria, we assumed a cumulative probability of failure at 25% at 48 weeks in the PI regimen group.

A total of 404 evaluable subjects, randomized in a 1:1 ratio to 2 treatment groups (202 subjects per treatment group), achieves at least 80% power to detect a non-inferiority margin of 1.606 in the hazard ratio, which corresponds to a 12% difference in the cumulative probability of failure rate between INI-based regimen group (37%) and PI-based regimen group (25%), with 97 events required. The sample size and power calculation assumes that the cumulative probability of failure is 25% for the PI regimen group and 23% for the INI-based regimen group (i.e. the expected hazard ratio is 0.909), using a non-inferiority margin of 1.606 in hazard ratio and a two-sided 95% confidence interval (CI). The sample size and power calculation were made using the statistical software package nQuery Advanced, non-inferiority testing of two survival curves using cox regression module (Version 8.1.2.0). With an estimated ~7.5% drop off rate/year, we plan to enroll 220 subjects per group to ensure we have sufficient power for this per-protocol analysis.

Superiority of INI-based regimen group versus PI-based regimen group will be evaluated after the non-inferiority is established. With an ITT analysis, 440 subjects and 78 events, a two-sided log-rank test at an alpha level of 0.05 will achieve at least 80% power to detect a 50% reduction in hazard rate in INI-based regimen (i.e. the hazard ratio is 0.5). A 50% reduction in hazard rate means that INI-based regimen could decrease the risk by 11.6% (25% for PI- vs 13.4% for INI- based regimen).

9.2 Planned recruitment rate

In the ANRS 146 OPTIMAL trial, in which similar patients were enrolled (late presenters with low CD4 cell count or ADE), 10% of screened patients were not eligible. Based on this information, we estimated that about 489 patients should be screened. Centres of NEAT ID Network with infectious disease units for inpatient and outpatient care will be the prioritised study sites of the LAPTOP Trial. We expect that about 45 sites in total across eight European countries. Therefore, we estimated that about 7-15 patients should be screened per site.

9.3 Statistical analysis plan

These analyses will assess the efficacy and safety of BIC containing regimen in comparison with the boosted PI containing regimen.

All randomised patients who received at least 1 time any study treatment will be included in the intent-to-treat (ITT) analysis population. Of note patients lost-to follow-up or violating the protocol will not be excluded from the ITT population. Patients who switch treatment to another will be analysed as if they are remained in their initial randomisation group. All participants who are lost to follow-up or discontinued the study when they are endpoint free at time of leaving the study will be censored at the time of leaving the study. We will use time-to-event methods, including Kaplan–Meier survival curves and Cox proportional-hazards models to account for all participants in the analysis. The per-protocol population will include all patients from the ITT population except those who did not fulfil the inclusion/exclusion criteria, who withdrew their consent, gave up, lost to follow-up or discontinued early study medication for any reasons other than any component of the primary endpoint.

9.3.1 Summary of baseline data and flow of patients

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation (SD), 1st quartile, median, 3rd quartile, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical variables.

The number of patients and the flowchart of the study will be presented. The period of enrolment and the total number of patients screened to be included in the study will be presented. The number of ineligible patients and the total number of randomised patients will be presented. The number of patients who never take the study treatment will also be presented by group and those who remained on the study treatment up to week 48 will be presented.

9.3.2 Primary outcome analysis

The primary outcome analysis will be performed with both ITT population and per-protocol population. The primary endpoint is the occurrence of a severe morbidity (virological failure; death related to HIV, AIDS, OI/severe BI or complications of therapy including IRIS; new ADE; new serious non-AIDS events; and clinically relevant AEs of any grade leading to study treatment discontinuation). The effect of study treatment will be assessed using Cox regression model with treatment group and adjustments for stratification factor (participating country and baseline CD4 cell counts). Separate

analyses for each component of the primary endpoint will be done. Kaplan-Meier curves will be plotted for the primary endpoint and its component.

9.3.3 Secondary outcome analysis

All secondary outcome analysis will be done with the ITT population. The p-values will be two-tailed, with a significant level of 0.05.

The proportion of patients with HIV-ribonucleic acid (RNA) viral load <50 copies/mL at week 48 will be analysed using the snapshot approach. Fisher's exact test will be used to compare the estimated proportion between the two groups.

A genotypic resistance test will be performed in all patients with virological failure. Drugs resistance mutations will be identified from the International AIDS Society (IAS)-USA resistance testing panel (last version at the time of analysis) and for BIC we will use IAS, Agence Nationale de Recherches sur le SIDA (National Agency for AIDS Research) (ANRS) or Royal College of Physicians (RCP) lists to perform the analysis whenever they will be made available. Resistance to BIC will also be identified using phenotypic resistance test. Fisher's exact test will be used to compare the presence of at least one drug resistance mutation between the 2 groups.

The median time to reach CD4 cell count >200/µl will be estimated using the Kaplan-Meier method, censoring at week 48 or last follow-up date if not seen at week 48. Time to reach CD4 cell count >200/µl will be defined as the time between the date of study treatment initiation (baseline, week 0) and the date of which patient reached CD4>200/µl. The log-rank test will be used to compare the two survival functions. The p-values will be two-tailed, with a significant level of 0.05. The proportion of patients with CD4 cell count <350/µl at week 48 will be done with the ITT population, with the last observation carried forward (LOCF) approach. Fisher's exact test will be used to compare the 2 groups.

The median change in CD4/CD8 ratio from baseline to week 48 will be analysed with the ITT population, with the LOCF approach. The non-parametric Mann Whitney test will be used to compare the change from baseline between the 2 groups.

The incidence of IRIS will be analysed with the Kaplan-Meier method. The Log-rank test will be used to compare the two survival functions. The effect of study treatment on IRIS will be assessed using Cox regression model with treatment group and adjustments for stratification factors.

The incidence of hospitalisation will be estimated by the Kaplan-Meier estimate. The Log-rank test will be used to compare the two survival functions. The duration of hospitalisation will be estimated by the cumulative days of hospitalisation during the course of study and will be compared between the 2 groups by using the Mann-Whitney test. The rate of relapse/recurrence will be estimated by the number of patients with relapse/recurrence divided by the total number patients in ITT population. Fisher's exact test will be used to compare the 2 groups.

The frequency of each Grade 2, 3 or 4 AEs, laboratory toxicities, and ART and OI/BI treatment changes and dose modifications due to toxicities and IRIS will be described and compared by group. Fisher's exact test will be used to compare the 2 groups.

The proportion of patients with health care resource use, and emergency room visits will be compared in the two groups with Fisher's exact test. The total inpatient days will be estimated by the cumulative inpatient days during the course of study and will be compared between the 2 groups by using the Mann-Whitney test.

To assess the impact of study treatment on the evolution of QOL at week 48, we will use multiple imputation approach to replace missing values. We will compare the treatment effect on QOL on each of the 5 datasets generated, including the imputed values, and the results will be combined with Rubin's rules. A generalized estimating equation (GEE) model will be used.

9.4 Subgroup analyses

Subgroup analyses for the primary endpoint will be done to explore whether estimated treatment effects vary significantly between subcategories of trial participants. The following variables will be assessed: age, gender, transmission group, ethnic group, baseline CD4 (<50, 50-199, ≥200), baseline viral load (<100,000, 100,000-500,000, >500,000), smoker, adherence (>/< 95%) and participating country. Heterogeneity of the treatment effect across subgroups will be assessed by including terms for interactions between treatment and subgroup variables in expanded Cox models. Age will be divided into three groups using tertiles/quartiles.

9.5 Interim analysis and criteria for the premature termination of the trial

No formal interim analysis will be done. However, a DSMB will be established and will review the data regularly during the course of the study (see Section 12 of the protocol for more details).

There is no trial-specific stopping criterion as the trial involves licensed products used within the marketing authorisation dosing instruction.

9.6 Subject population

All randomised patients who received at least 1 time any study treatment will be included in the ITT analysis population. Of note patients lost-to follow-up or violating the protocol will not be excluded from the ITT population.

The per-protocol population will include all patients from the ITT population except those who did not fulfil the inclusion/exclusion criteria, who withdrew their consent, gave up, lost to follow-up or discontinued study medication for any reasons other than study endpoint criteria.

9.7 Procedure(s) to account for missing or spurious data

To assess the impact of study treatment on the evolution of QOL at week 48, we will use multiple imputation approach to replace missing values. We will compare the treatment effect on QOL on each of the 5 datasets generated, including the imputed values, and the results will be combined with Rubin's rules. A GEE model will be used. LOCF approach will be used to replace missing CD4 and CD8 values.

9.8 Other statistical considerations

All deviations from the statistical analysis plan will be recorded during the conduct of the analysis. If there is a decision for major modifications to the statistical analysis while the clinical trial is in progress, this will be part of a protocol amendment.

10 DATA HANDLING

10.1 Data collection tools and source document identification

10.1.1 Source Data

Source data will be all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and

evaluation of the trial. Source data are contained in the source documents (original records or certified copies) maintained at site.

10.1.2 Source Documents

Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial) will be maintained at site.

The subject's number and date of entry into the study, along with a study identifier, should be recorded in the subject's study records. The following should also be recorded in the study records; confirmation of written and verbal consent, the subject's clinical status, date of every study visit, date study medication was started and stopped, concomitant medications, copies of all relevant reports and laboratory tests, comments on results and reference to any AEs.

Source documents include, but are not limited to, participant medical records, SAE and reportable event forms (see section 8), questionnaires, laboratory reports, participant progress notes, pharmacy records and any other reports or records of procedures performed in accordance with the protocol.

10.1.3 Case report forms

Subject data collected during the study will be recorded in a web-based electronic CRF (eCRF). In order to maintain confidentiality, the subject information will be pseudo-anonymised.

The design of CRFs will ensure that:

- adequate collection of data has been performed
- proper paper trails can be kept to demonstrate the validity of the trial (both during and after the trial)
- only the data required by the protocol are captured in the CRF (using the CRF to capture secondary data not required for the study may be a criminal beach of the Data Protection Act, makes the CRF unnecessarily complicated, and can make it more difficult to extract the primary data for analysis)

Data required for the study will be recorded in an eCRF collection tool by appropriately trained and authorised member(s) of the study team who must be identified and authorised in writing by the PI before they conduct any study related tasks. A delegation of responsibility log identifying who can enter data and/or sign off a CRF will be maintained by the PI.

The eCRF should be kept current by entering data ideally within 7 working days of collection to enable the study monitor to review the subject status throughout the course of the study. In the case of the eCRF being unavailable, a paper CRF can be made available to use at site.

The data will be reviewed and approved by the Investigator following subject completion.

10.2 Data handling and record keeping

The Study Monitor and Data Manager will review data on an on-going basis and raise any discrepancies with site staff as required.

At the end of the study, the site will be provided with copies of their CRFs for filing in the ISF before the eCRF is decommissioned, ensuring site access to their data at all times.

Data extracted from the eCRF will be kept on a secure network drive of the sponsor with access to authorised personnel of the Biometrics Team only.

The data is pseudo-anonymised at all times and is transferred securely using an encrypted file share process. All transfers are fully documented.

10.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

10.4 Archiving

Following completion of the study, subject records, CRF and other study documentation will be retained by the Investigator in accordance with GCP and applicable regulatory requirements.

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g. for sponsor or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- The ISFs must be retained for a minimum of 5 years from the date of the final CSR. Sponsor will inform the investigator of the retention period due date at the time when this CSR (or equivalent) is issued to the site.
- The investigator must notify sponsor of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

Archiving will be authorised by the Sponsor following submission of the end of study report.

The sponsor will be responsible for archiving the Trial Master File (TMF). The Investigators at site(s) will be responsible for the retention/archiving of subject records, CRF, ISF and other study documentation (as applicable) in accordance with GCP and applicable regulatory requirements.

Destruction of essential documents will require authorisation from the Sponsor in writing.

The trial database will be maintained and stored in accordance with GCP.

11 MONITORING, AUDIT & INSPECTION

A risk-based monitoring plan will be followed for this study based on the trial risk assessment. The plan will detail monitoring frequency, requirements and processes.

The purpose of monitoring is to verify the rights and wellbeing of human subjects are protected; that trial data is accurate, complete and verifiable with source data; that the trial is conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

A monitor will conduct regular site visits for the purpose of monitoring various aspects of the study. The Investigator must agree to allow the study monitor and authorised representatives of the Sponsor, to inspect all CRF and corresponding source documents, e.g. original medical records, subject records and laboratory raw data, access to the clinical supplies, dispensing and storage areas and agree to assist with their activities if requested. The Investigator should provide adequate time and space for monitoring visits.

The monitor will query any missing or spurious data with the Investigator, which should be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, the monitor's signature and Investigator's or designee's confirmation signature.

For the purpose of compliance with GCP and regulatory agency guidelines, it may be necessary for sponsor authorised Quality Assurance personnel and/or authorised personnel from an external regulatory agency to conduct an audit/inspection of an Investigational site. The purpose of an audit is to assess the quality of data with regard to accuracy, adequacy and consistency, and to assure that studies are in accordance with GCP, and Regulatory Agency guidelines. Having the highest quality data from studies is an essential aspect of drug development.

The Investigator will be given sufficient notice to prepare for such visits, which are planned to take usually between one and two days and may be conducted at any stage during the study. The audit will involve the review of all study related documentation, which is required by GCP to be maintained by each site, review of drug storage, dispensing and return, review of all study related supplies and review of source documents against the CRF to assure the adequacy and accuracy of the information which has been recorded, including the verification of any AE which have occurred.

12 ROLES AND RESPONSIBILITIES OF TRIAL OVERSIGHT COMMITEES/ GROUPS & INDIVIDUALS

Three main trial management groups will be involved in the set up and management of the clinical trial.

Trial Steering Committee (TSC)

The TSC members should meet to periodically review the safety data and will liaise with the DSMB regarding any safety issues. The TSC must have a majority independent representation, including the Chair.

Data Safety Monitoring Board (DSMB)

The DSMB is the group that monitors the main safety and efficacy outcome measures and the overall conduct of the trial, with the aim of protecting the safety and interests of the trial participants.

The DSMB will meet periodically to review unblinded data. The frequency of these meetings will be detailed in a separate document, the DSMB Charter, but are planned to take place on a quarterly basis as a minimum.

Endpoint Committee

The DSMB or TSC may request the endpoint review committee meet to review the trial endpoints to determine trial outcomes.

Trial Management Group (TMG)

The TMG should meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them.

The membership, frequency and the study aspects to be reviewed by the above groups, will be outlined in a separate document.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC) review & reports

The study will comply with the following requirements

- Before the start of the trial, approval will be sought from an IRB/IEC for the trial protocol, ICFs and other relevant documents e.g. advertisements and GP information letters
- Substantial amendments that require review by IRB/IEC will not be implemented until the IRB/IEC grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the CAs before they can be implemented in practice at sites)
- All correspondence with the IRB/IEC will be retained in the TMF/ISF
- An annual progress report (APR) will be submitted to the IRB/IEC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- It is the CI's responsibility to produce the annual reports as required
- The CI will notify the IRB/IEC of the end of the study
- If the study is ended prematurely, the CI will notify the IRB/IEC, including the reasons for the premature termination
- Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the IRB/IEC

13.2 Peer review

The high-quality peer review process (initiated by study sponsor) for the trial protocol will meet the following review criteria:

a) **Independent**: At least two individual experts will review the study. Reviewers are external to the investigators' host institution and not involved in the study in any way.

b) **Expert**: Reviewers will have knowledge of the relevant discipline to consider the clinical and/or service-based aspects of the protocol, and/or have the expertise to assess the methodological and statistical aspects of the study.

c) **Proportionate**: Peer review commensurate with the size and complexity of the study.

13.3 Regulatory Compliance

This study will comply with the following:

- the trial will not commence until a Clinical Trial Authorisation (CTA) is obtained as required by local regulations
- the protocol and trial conduct will comply with the Clinical Trial Regulation (EU) No 536/2014 and local regulations applicable to each country

13.4 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the CI and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

13.5 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity or rights of the subjects of the trial; or
(b) the scientific value of the trial and the reliability and robustness of the data generated in the trial

Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

The sponsor will notify the licensing authority in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) Clinical Trial Regulation; or
(c) the protocol relating to that trial, as amended from time to time, within 7 calendar days of becoming aware of that breach

13.6 Data protection and patient confidentiality

All data collected during the trial will be processed in agreement with the requirements set forth in applicable national data protection laws and in compliance with the General Data Protection Regulation (Regulation EU 2016/679) (GDPR), the UK Data Protection Act 2018 (DPA 2018), and the UK GDPR. All investigators and investigator site staff will comply with the data protection requirements applicable to the country in which they are conducting trial activities.

The security of personal data collected in the trial will be upheld using the following technical and organisational measures:

- Participant data will be pseudo-anonymised by replacing the information that identifies the participant with a unique identifier (pseudonym) at the point of enrolment. Datasets sent to data processors and third parties authorised by the Sponsor to process personal data will no longer be attributable to a specific participant without the use of additional information.
- The link between the unique identifier and the participant's identity will be securely maintained at the investigator site, accessible by authorised personnel only. The link may be

made available to regulatory agencies for the purposes of audits or inspections, or to study monitors authorised by the Sponsor to monitor the trial.

- It is the responsibility of the investigator to protect the identity of the participant, and the security of personal data held at site should be maintained per local technical and organisational measures.
- Trial data will be stored in a secure electronic data capture system (EDC) overseen by the CRO. The EDC system is protected by high levels of physical and cyber security. The EDC meets the requirements for the storage of personal data. The data will be stored on a secure / backed up network accessed by authorised personnel only. A log of authorised personnel with access permissions is maintained centrally.
- Only sufficiently trained and delegated personnel will have access to the EDC.
- Pseudonymised data will be used for statistical analysis. The statistical analysis will produce an aggregated output rendering the data anonymous. Only the anonymous statistical analysis output will be used for the trial results reporting.
- At the end of the trial, the EDC will be decommissioned and the pseudonymised data will be securely maintained in the archived TMF for the remainder of the retention period. The TMF retention period is 25 years from the end of the trial in line with the Clinical Trials Regulation (Regulation EU No 536/2014).
- At the end of the trial, each clinical trial site will receive a copy of the case report forms of the participants recruited at that site only, for archiving purposes in line with their own standard operating procedures. The protection of these data remains the responsibility of the investigator.
- Data collection will be kept to the minimum required to answer the objectives of the trial.
- The privacy and confidentiality of personal data on stored samples will be protected by the same standards applicable to all other clinical trial data.

In the event of a data security breach, the investigator or site staff will report the incident to the Data Protection Officer of the sponsor (dpo@neat-id.org). The severity of the risk will be assessed to determine reporting requirements per relevant data protection legislation. It remains the responsibility of the Sponsor to report applicable data breaches to the relevant Data Protection Authority(ies). Depending on the result of this assessment, the participant(s) to whom the breach relates may be informed. A Corrective and Preventative Action review may also be performed to reduce the risk of future data security breaches.

13.7 Indemnity

The Sponsor will undertake indemnity and insurance cover for this trial.

13.8 Amendments

The sponsor may make a non-substantial or substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the sponsor will submit a valid notice of amendment to the appropriate IRB/IEC, trial registries, and regulatory agencies. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial.

13.9 Post trial care

Post study medication will not be provided to participants. Following study completion patients will receive treatment as per local standard of care.

13.10 Access to the final trial dataset

The investigators will be provided reasonable access to statistical tables, figures, and relevant reports.

Sponsor will also provide the investigators with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with sponsor policies.

14 DISSEMINATION POLICY

Whole or part of this study results will be communicated, orally presented, and/or published in appropriate scientific journals. Full anonymity of subject's details will be maintained throughout. Subjects wanting to see the results of the trial can request a copy of the article from the investigators once it has been published.

Preliminary data review and analysis may be conducted on the main study cohort or a sub study cohort throughout the study duration and may be presented in scientific presentations in both national and international conferences and publication.

The data generated in the study will be submitted to a relevant medical journal according to criteria set out in The International Committee of Medical Journal Editors (www.icmje.org) who recommends that;

i. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
ii. Drafting the work or revising it critically for important intellectual content; AND
iii. Final approval of the version to be published; AND
iv. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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APPENDIX 1 - STUDY FLOWCHART

Procedures	Screening Visit	Baseline Visit	Treatment Phase						Follow Up/Early Termination Visit
	Day -28 to Enrolment[1]		Week 4 (± 7 days)	Week 8 (± 7 days)	Week 12 (± 7 days)	Week 24 (± 7 days)	Week 36 (± 7 days)	Week 48 (± 7 days)	30 days following Week 48 visit (± 7 days)
Informed consent	•								
Eligibility assessment[3]	•								
Demographics	•								
Medical and social history[4]	•								
ECG[5]	•								
HBV and HCV testing[6]	•								
Latent TB test[7]	•								
Local Resistance testing [8]	•								•
Randomisation		•							
Symptom-directed physical examination		•	•	•	•	•	•	•	•
Vital signs[9]	•	•	•	•	•	•	•	•	•
Urinalysis[10]		•			•	•	•	•	•
Haematology (including CD4 & CD8 testing)[11]	•	•	•	•	•	•	•	•	•
Clinical chemistry[12]	•	•	•	•	•	•	•	•	•
Viral load testing[13]	•	•	•	•	•	•	•	•	•
Sample collection for central resistance testing (deep sequencing)[14]		•	•	•	•	•	•	•	•
Concomitant medications	•	•	•	•	•	•	•	•	•
Adverse event assessments		•	•	•	•	•	•	•	•
Quality of Life questionnaire (EuroQoL EQ-5D-3L)		•	•	•	•	•	•	•	•
HIV Symptom Index questionnaire (HIV-SI/SDM)		•	•	•	•	•	•	•	•
Dispensing of trial drugs[15]		•			•	•	•		
Adherence[16]					•	•	•	•	
Serum pregnancy test[17]	•								
Urine pregnancy test[18]		•	•	•	•	•	•	•	•
Physical examination (including height & weight)[19]	•	•	•	•	•	•	•	•	

	Assessment sub notes	Parameters/Notes
1	Screening visit	The maximum time between screening visit and baseline visitis 28 days; however, participants should be invited for their baseline visit as soon as reasonably possible in order to start their treatment. . Only the following laboratory assessments are required for screening and historic (up to 28 days old) tests results may be used for screening: • HBV and HCV testing • TB test • CD4 & CD8 testing • Platelet count testing • Clinical chemistry (only creatinine, creatinine clearance, eGFR, potassium, sodium, ALT, AST is required) • Viral load testing • Resistance testing (the last resistance test carried out can be used) A serum pregnancy test is mandatory at the screening visit for women of child bearing potential
2	Baseline Visit	For baseline results, all screening tests carried out within 10 days before baseline can be used. This includes historic screening results, as long as they fall within the 10 day window before baseline. Screening data obtained more than 10 days from baseline, must be repeated at baseline.
3	Eligibility	According to the inclusion/exclusion criteria.
4	Medical & social history	Including: • Recreational drug use • Smoking history • Alcohol intake • Concomitant diseases • Past & present medical history, including HIV- associated conditions • Review of any medication taken within the last 30 days
5	ECG	12-Lead ECG performed supine. If an ECG is not performed at screening, it must be performed by the time of the baseline visit.
6	HBV & HCV testing	HBV antigen test and hepatitis C (HCV) antibodies test (if patient tests positive for HCV antibodies, test for HCV RNA, if positive and chronic for either HBV or HCV, add HBV DNA test at baseline visit). HBV test to be repeated in event of positive result. Participants with active HBV infection at study entry will be monitored throughout the study and additional HBV DNA tests performed at the Week 24 and 48 visits. For screening, test results 28 days prior to the screening visit can be used
7	Latent TB Testing	A Latent TB test (IGRAs e.g. ELISPOT, QuantiFERON) may be performed in **patients with expected latent TB** at the screening visit. For screening, test results 28 days prior to the screening visit can be used. Patients can be randomised into the study without having the latent TB screening results available at randomisation A TB test can be performed at subsequent visits because of clinical suspicion.

	Assessment sub notes	Parameters/Notes
8	Resistance testing (performed locally)	A local resistance test will be performed at the screening visit. This result is not required for eligibility or prior to randomisation. If a HIV resistance test was done previously and results are available, the last resistance test carried out shall be considered. An additional resistance test will be performed at the ETV for patients with virological failure or insufficient virological response.
9	Vital Signs (10 mins resting)	Including: • Pulse • Blood pressure
10	Urinalysis	Including: • Urinary creatinine* (not mandatory if ACR and PCR are available) • Albumin: Creatinine Ratio (ACR)* and Protein: Creatinine Ratio (PCR)* – mandatory if urinary creatinine not available • Urinary glucose (dipstick test sufficient)* • Urinary proteins* • Albumin (can be obtained from 'spot' urine test)* • Nitrites (dipstick test sufficient) • Urinary phosphate • Beta-2 microglobulin • Leukocytes (dipstick test sufficient) * Assessments should be performed as per local site procedure; however, assessments marked with an asterisk are mandatory for the study at the visits required in the table.

	Assessment sub notes	Parameters/Notes
11	Haematology (non-fasting)	Including: • Platelet count* • RBC Count (indices MCV & MCH)* • WBC count (absolute)* • CD4 Count and %* (CD4 count can be calculated from % and total lymphocytes) • CD8 Count and %* (CD8 count can be calculated from % and total lymphocytes) • Haemoglobin* • Haematocrit* RBC Count indices: • MCV • MCH Automated WBC differentials: • Neutrophils* • Lymphocytes* • Monocytes • Eosinophils • Basophils * Assessments should be performed as per local site procedure; however, assessments marked with an asterisk are mandatory for the study. Assessments that have been underlined are required at screening (results up to 28 days old can be used).

	Assessment sub notes	Parameters/Notes
12	Clinical chemistry (non-fasting)	• Urea* • Chloride* • Alkaline phosphatase* • Creatine phosphokinase* • Creatinine* • Calcium* • Phosphate* • Creatinine clearance, eGFR* (Calculations: Cockcroft-Gault (requires weight), MDRD, CX-Epi) • Glucose* • Total* and indirect bilirubin • Potassium* • Total protein* • Sodium* • ALT* • AST* • Albumin* • Cholesterol* • HDL* • LDL* • Triglycerides* * Assessments should be performed as per local site procedure; however, assessments marked with an asterisk are mandatory for the study at and after baseline. Assessments that have been underlined are required at screening (results up to 28 days old can be used).
13	Viral load testing	HIV RNA viral load results obtained 28 days prior to screening can be used.
14	Resistance testing for deep sequencing (sent to central laboratory)	In addition to the resistance test performed locally, a resistance testing sample will be taken at the Baseline visit, each visit in the treatment phase (Week 4, 8, 12, 24, 36 and 48) and at the ETV (for patients with virological failure identified outside of a scheduled visit. All resistance testing samples for patients with virological failure will be sent to a central laboratory for next generation sequencing to look for low-level pre-existing resistance in cases of suspected resistance development.
15	Drug dispensing	There will be four dispensations of the study medication to the patient (Baseline visit, Week 12, 24 and 36).
16	Adherence	Also performed at the ETV if required.
17	Serum pregnancy test	For women of child bearing potential only (see Appendix 7 for definition).
18	Urine pregnancy test	Dipstick and urine pregnancy test (WOCBP only - see Appendix 7 for definition). This is a mandatory assessment. If a urine pregnancy test is not possible, a serum pregnancy test can replace this.
19	Physical examination	Weight is required at all visits, as detailed in the appendix 1, however height is only required at baseline.

APPENDIX 2 – AIDS CLINICAL TRIAL GROUP (ACTG) GRADING SCALE

DAIDS AE Grading Table Corrected Version 2.1-July 2017

Attached as a separate document and available online at:
https://rsc.tech-res.com/docs/default-source/safety/daidsgradingcorrecetedv21.pdf?sfvrsn=6

APPENDIX 3 – AIDS-DEFINING CONDITIONS

From CDC, available at https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2.htm

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision) †
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii,* disseminated or extrapulmonary†
- *Mycobacterium tuberculosis* of any site, pulmonary, †§ disseminated, † or extrapulmonary†
- *Mycobacterium*, other species or unidentified species, disseminated† or extrapulmonary†
- *Pneumocystis jirovecii* pneumonia†
- Pneumonia, recurrent†§
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month†
- Wasting syndrome attributed to HIV

* Only among children aged <13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12].)

† Condition that might be diagnosed presumptively.

§ Only among adults and adolescents aged ≥13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17].)

APPENDIX 4 - INISIGHT SERIOUS NON-AIDS EVENTS CRITERIA

Version 4, August 2012

ACUTE MYOCARDIAL INFARCTION

A. Rise and/or fall of cardiac biomarkers (preferably troponin), with at least one value above 99th percentile of upper reference limit (URL)

B. Occurrence of a compatible clinical syndrome, including symptoms (such as chest pain) consistent with myocardial ischemia

C. ECG changes indicative of new ischemia (new ST-changes or new left bundle branch block [LBBB]), or development of pathological Q waves on the ECG

D. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

E. Sudden unexpected cardiac death involving cardiac arrest before biomarkers are obtained or before a time when biomarkers appear, along with (1) new ST-changes or new LBB, or (2) evidence of fresh thrombus on coronary angiography or at autopsy

F. In patients with percutaneous coronary interventions and normal baseline troponin, increases in troponin of three times the 99th percentile of URL

G. In patients with coronary artery bypass grafting and normal baseline troponin, increases in troponin of five times the 99th percentile of URL PLUS at least one of the following: (1) new pathological Q-waves or new LBBB, (2) angiographically documented new graft or native artery occlusion, or (3) imaging evidence of new loss of viable myocardium

H. Pathologic findings of acute myocardial infarction (including acute MI demonstrated as the cause of death on autopsy)

I. Development of 1) evolving new Q waves, or 2) evolving ST elevation, preferably based on at least 2 ECGs taken during the same hospital admission

J. In patients with coronary artery bypass grafting and normal baseline troponin, increases in troponin of five times the 99th percentile of URL

Confirmed: One of the following 5 criteria (adapted from 2007 Universal Definition of Myocardial Infarction):
1. A + (B or C or D)
2. E
3. F
4. G
5. H

Probable: B+I or J

CONGESTIVE HEART FAILURE

A. Clinical signs and symptoms compatible with left or right sided heart failure (e.g., paroxysmal nocturnal dyspnea, rales or S3 on auscultation, jugular venous distention) without an alternative explanation

B. Hemodynamic measurements, radionucleotide ventriculography, echocardiogram, cardiac catheterization, or multiple gated acquisition scan showing a decreased ejection fraction of < 45%

C. Echocardiogram, cardiac catheterization or other studies showing evidence of increased left atrial pressure or right heart failure

D. Elevated levels of Brain Natriuretic Peptide (BNP) or NT-proBNP

E. Chest x-ray or other imaging study showing evidence of congestive heart failure, including cardiac enlargement

F. Documentation of treatment for congestive heart failure

Confirmed: (A+B) or (A+C) or (A+D)
Probable: A+E+F

CORONARY ARTERY DISEASE REQUIRING DRUG TREATMENT

A written report in the medical record documenting:

A. Evidence of myocardial ischemia based on either diagnostic imaging (such as a stress echocardiogram or thallium scan) or diagnostic changes on an electrocardiogram (such as during stress testing or an episode of chest pain)

B. Evidence of coronary artery disease based on coronary angiography or other diagnostic imaging

C. Other evidence of myocardial ischemia and/or coronary artery disease (including that based primarily upon symptoms and clinical presentation, such as chest pain with exertion)

D. Use of medication given to treat or prevent angina (e.g., nitrates, beta blockers, calcium channel blockers)

Confirmed: (A or B) + D
Probable: C+D

CORONARY REVASCULARIZATION

Confirmed: A procedure report, hospital discharge summary, or other medical record from the hospitalization during which the procedure was performed for treatment of coronary artery disease (including coronary artery bypass graft, coronary artery stent implant, coronary atherectomy, and percutaneous transluminal angioplasty), or a consultation note from the participant's cardiologist documenting the occurrence of the procedure

Probable: Not applicable

DECOMPENSATED LIVER DISEASE

A. Histologic, radiographic, or ultrasound evidence of cirrhosis, as documented by one of the following:

1. Histologic evidence of cirrhosis obtained by liver biopsy or autopsy

2. MRI or CT consistent with cirrhosis
3. A positive result on transient elastography (FibroScan) or other ultrasound imaging consistent with cirrhosis

B. Clinical evidence of decompensation, as documented by one of the following, and without an alternative explanation:

1. Ascites
2. Hepatic encephalopathy
3. Bleeding from gastric or esophageal varices
4. Spontaneous bacterial peritonitis

Confirmed: A+B
Probable: B

DEEP VEIN THROMBOSIS

A. Diagnosis of deep vein thrombosis (DVT) by contrast venography, helical computed tomography, MRI, or ultrasonography other comparable imaging techniques

B. An elevated D-dimer test OR abnormal plethysmography

C. A score on the Wells Clinical Prediction Rule for DVT of ≥ 3 points

D. Absence of alternative diagnosis as likely or greater than that of deep venous thrombosis

Wells Clinical Prediction Rule for DVT
One point for each of the following:

- Active cancer (treatment ongoing or within previous 6 months, or palliative)
- Paralysis, paresis, or plaster immobilization of lower extremities
- Recently bedridden for more than 3 days, or major surgery, within 4 weeks
- Localized tenderness along distribution of the deep venous system
- Entire leg swollen
- Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)
- Pitting edema (greater in the symptomatic leg)
- Collateral superficial veins (non-varicose)

(Adapted from: Wells PS et al. Lancet 1997;350:1796)

Confirmed: A
Probable: B+C+D

DIABETES MELLITUS

A. Classic symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose concentration >=200 mg/dl (11.1 mmol/l). (Classic symptoms include polyuria and polydipsia; Random is defined as any time of day without regard to last meal)

B. 2-hour plasma glucose >=200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water).

C. Repeated abnormal fasting plasma glucose (FPG) and/or abnormal Haemoglobin A1C level (HA1C) results using the following criteria:

1. FPG >=126 mg/dl (7.0 mmol/l) on at least two different dates (Fasting is defined as no caloric intake for at least 8 hours).
2. HA1C >=6.5% on at least two different dates
3. An FPG >=126 mg/dl (7.0 mmol/l) PLUS a HA1C >=6.5%, with these tests performed on two different dates

D. Documentation of taking an approved anti-diabetic medication to lower glucose levels in the blood, such as insulin or oral hypoglycaemic agents.

E. A single abnormal FBS OR a single abnormal HA1C

Confirmed: A or B or C
Probable: D
Possible: E

END-STAGE RENAL DISEASE

A. Haemodialysis or peritoneal dialysis documented in a clinical note for a period of at least three months

B. A kidney transplant documented in a clinical note

C. Haemodialysis or peritoneal dialysis documented in a clinical note for a period of at least one month and up to the time of death in a patient who dies within three months after dialysis begins

Confirmed: A or B
Probable: C

NON-AIDS-DEFINING CANCER

A. Diagnosis of cancer other than lymphoma, Kaposi's sarcoma (KS), or invasive cervical cancer in an autopsy report

B. Diagnosis of cancer other than lymphoma, KS, or invasive cervical cancer in a pathology report that established the diagnosis

C. Diagnosis of cancer other than lymphoma, KS, or invasive cervical cancer in a hospital discharge summary or consultation note from the hospitalization or clinic visit during which the diagnosis was established

Confirmed: A or B
Probable: C

PERIPHERAL ARTERIAL DISEASE

A. Compatible clinical signs and symptoms (e.g., intermittent claudication, femoral bruit, decreased peripheral pulses, change in colour or temperature of limb suggesting peripheral arterial disease)

B. Positive results on diagnostic imaging studies (e.g., Doppler ultrasound, contrast arteriography, MRI arteriography)

C. Ankle Brachial Pressure Index < 0.90 in non-diabetics

D. A procedure report, hospital discharge summary, or other medical record from the hospitalization during which the procedure was performed documenting an invasive procedure for treatment of peripheral arterial disease (e.g., percutaneous transluminal angioplasty, endovascular procedures, or vascular surgery), or a consultation note documenting the occurrence of the procedure

Confirmed: (A+B) or (A+C) or D
Probable: A

PULMONARY EMBOLISM

A. Symptoms compatible with pulmonary embolism, such as shortness of breath, chest pain, or haemoptysis

B. Results consistent with a diagnosis of pulmonary embolism on pulmonary angiography, helical CT, ventilation-perfusion scan or other comparable imaging studies

C. A diagnosis of pulmonary embolism on autopsy
D. Results consistent with a diagnosis of deep venous thrombosis on venography, ultrasound, or other comparable imaging studies

E. A chest x-ray which, if performed, does not suggest an alternative aetiology for the symptoms described in criteria A

Confirmed: (A+B) or C
Probable: A+D+E

STROKE

A. Acute onset with a clinically compatible course, including unequivocal objective findings of a localizing neurologic deficit

B. CT or MRI compatible with diagnosis of stroke and current neurologic signs and symptoms

C. Stroke diagnosed as cause of death at autopsy

D. Positive lumbar puncture compatible with subarachnoid haemorrhage

E. Death certificate or death note from medical record listing stroke as cause of death

Confirmed: (A+B) or C
Probable: (A+D) or (A+E)

APPENDIX 5 - INSIGHT PROGRESSION OF HIV DISEASE CRITERIA

Version 2.0, September 2010

	CONFIRMED	PROBABLE
CONSTITUTIONAL DISEASE		
HIV wasting syndrome	None	A plus B plus C: (A) unexplained, involuntary weight loss >10% from baseline, (B) persistent diarrhea with > 2 liquid stools/d for > 1 month or weakness for > 1 month or fever for > 1 month, (C) tests for alternate causes of weight loss, such as cancer, TB, MAC, cryptosporidiosis or other specific causes of weight loss, if obtained, should be negative
INFECTIONS		
Aspergillosis, invasive pulmonary	A plus B plus C: (A) CXR abnormality compatible with aspergillosis, (B) invasive mycelia consistent with Aspergillus on lung biopsy, (C) positive culture from lung biopsy or sputum collected by any method	A plus B: (A) CXR abnormality compatible with aspergillosis, (B) invasive mycelia consistent with Aspergillus on lung biopsy or positive culture of lung tissue or positive culture of sputum collected by any method
Aspergillosis, other invasive	A plus B plus C: (A) compatible clinical course, (B) invasive mycelia consistent with Aspergillus on tissue biopsy or clinical evidence of infection, (C) positive culture from the affected tissue	A plus B: (A) clinical evidence of invasive infection, (B) invasive mycelia consistent with Aspergillus on tissue biopsy or positive culture at a normally sterile site (e.g., blood) apart from the involved tissue
Bartonellosis	A plus B: (A) Clinical or histologic evidence of bacillary angiomatosis or bacillary peliosis, (B) a positive culture or PCR for *B. quintana* or *B. henselae*	A plus B: (A) Clinical evidence of bacillary angiomatosis or bacillary peliosis, (B) positive silver stain for bacilli from a skin lesion or an affected organ
Candidiasis of bronchi, trachea, or lungs	Macroscopic appearance at bronchoscopy or autopsy plus microscopic evidence of yeasts or pseudo hyphae	None
Candidiasis, esophageal	A plus B: (A) Macroscopic appearance at esophagoscopy or autopsy, (B) microscopic evidence of yeasts or pseudo hyphae	A plus B plus C: (A) Recent onset of retrosternal pain or difficulty on swallowing, (B) a clinical diagnosis of oral candidiasis, endoscopic visualization of candidiasis and/or microscopic evidence of yeasts or pseudo hyphae from oropharyngeal mucosa, (C) clinical response to treatment

	CONFIRMED	PROBABLE
INFECTIONS (CONTINUED)		
Chagas disease (American trypanosomiasis) of the CNS	Histologic evidence obtained by brain tissue biopsy or autopsy	A plus B plus C plus D: (A) Focal, typically hemispheral neurological dysfunction with onset over several days or weeks; (B) enhancing focal lesion(s) with mass effect, and surrounding edema and contrast enhancement, typically located in grey matter; (C) serum antibodies to *T. cruzi*, (D) response to standard therapy with documented clinical or radiographic improvement (if radiography was done, it must be improved), or peripheral blood smear or CSF smear positive for *T. cruzi*
Coccidioidomycosis, disseminated or extrapulmonary	From tissue other than lung or hilum, A or B or C: (A) Microscopic demonstration of spherules, (B) positive culture, (C) antigen detection	None
Cryptococcosis, meningitis or extrapulmonary	From tissue other than lung or hilum, A or B or C or D: (A) microscopic demonstration of narrow based budding yeast, (B) for meningitis, if done, a positive CSF India ink test, (C) positive culture, (D) antigen detention	None
Cryptosporidiosis	Diarrhea for > 1 month and positive microscopy	None
CMV retinitis	Autopsy demonstration	Typical appearance on fundoscopy of discrete patches of retinal whitening, spreading along blood vessels, associated with vasculitis, hemorrhage and necrosis, confirmed by ophthalmologist
CMV radiculomyelitis	Autopsy demonstration	A plus B plus C plus D plus E plus F: (A) Loss of sensation, leg weakness, or decreased reflexes, (B) presentation over 3 days to 3 weeks, (C) CT, MRI or myelogram must be done and all imaging studies must not show a mass lesion, (D) CSF shows > 10 WBC with > 50% polymorphs, (E) CSF shows no other pathogen, (F) persistence of symptoms in the absence of CMV treatment, or elevated quantitative CMV in the CSF by PCR

	CONFIRMED	PROBABLE
INFECTIONS (CONTINUED)		
CMV meningoencephalitis	Autopsy or brain biopsy demonstration	A plus B: (A) Rapid < 4 weeks syndrome with progressive delirium, cognitive impairment and fever, (B) CT/MRI demonstration of periventricular abnormalities or elevated quantitative CMV DNA in the CSF by PCR
CMV, other disease	A plus B plus C plus D: (A) compatible illness, (B) histologic demonstration of inclusion bodies from affected tissue, (C) if done, detectible CMV antibodies, (D) if done, detectible CMV DNA or CMV antigen in blood	A plus B plus C plus D: (A) Compatible illness, (B) moderate to markedly high CMV antigen or CMV DNA in blood, (C) response to therapy, (D) if done, detectible CMV antibodies
HSV mucocutaneous ulceration	A plus B: (A) Ulceration for > 1 month, (B) histology, culture, PCR, or detection of antigen from affected tissue	A plus B: (A) Typical HSV ulceration for > 1 month, (B) response to an antiviral active against HZV unless resistance is demonstrated
HSV, bronchitis, pneumonitis, esophagitis, or other visceral disease	A plus B: (A) Compatible symptoms, (B) histology, culture, PCR, or detection of antigen from affected tissue	None
HZV, disseminated	A plus B: (A) multiple ulcerated lesions affecting at least 2 non-contiguous dermatomes, or with generalized cutaneous dissemination; or HZV involvement of the lung, liver, brain, or other internal organs (B) positive culture, PCR, or antigen assay from affected tissue	A plus B: (A) multiple typical ulcerated lesions affecting at least 2 non-contiguous dermatomes, or with generalized cutaneous dissemination (B) response to an antiviral active against HZV unless resistance is demonstrated
Histoplasmosis, disseminated or extrapulmonary	A plus B: (A) Compatible symptoms, (B) histology or culture or elevated blood or urine antigen levels	None
Isosporiasis	Diarrhea for > 1 month, plus microscopic identification of *Isospora belli*	None
Leishmaniasis, visceral	Compatible symptoms, plus microscopic identification of Leishmania	Compatible symptoms, plus a positive PCR test for Leishmania
Microsporidiosis	Diarrhea for > 1 month plus Microscopic identification of Microsporidia	None

	CONFIRMED	**PROBABLE**
INFECTIONS (CONTINUED)		
MAC and other mycobacterial disseminated disease	A plus B: (A) Fever, fatigue, anemia or diarrhea, (B) positive culture from blood, body fluids or tissue other than pulmonary, hilar or stool	A plus B plus C: (A) Fever, fatigue, anemia or diarrhea, (B) AFB or positive direct MAC PCR in blood, body fluids or tissue other than pulmonary, hilar or stool (C) no concurrent non-pulmonary TB
M. tuberculosis disease, pulmonary	A plus B: (A) Compatible symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) culture or PCR from sputum or bronchial lavage or lung tissue	A plus B plus C plus D: (A) Symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) abnormal chest X-ray, (C) AFBs seen in sputum or lavage or lung tissue but not grown in culture, (D) responds to treatment **POSSIBLE (pulmonary TB only)** A plus B plus C plus D: (A) Symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) abnormal chest X-ray compatible with pulmonary TB (such as upper lobe cavitation, pleural exudate), (C) No other etiology for pulmonary symptoms and signs identified, (D) Responds to anti-tuberculosis treatment
M. tuberculosis disease, extrapulmonary	A plus B: (A) Compatible symptoms, (B) culture or PCR from blood or affected tissue	A plus B plus C: (A) Compatible symptoms, (B) AFBs seen from affected tissue or blood (C) concurrent diagnosis of pulmonary TB or responds to treatment
Nocardiosis	Clinical evidence of invasive infection plus a positive culture from the affected tissue or blood	Clinical evidence of invasive infection plus microscopic evidence of bronchial weakly acid-fast organisms from the affected tissue
Penicillium marneffei, disseminated	Culture from a non-pulmonary site	Known presence in a *P. marneffei* endemic area plus characteristic skin lesions plus response to antifungal therapy for penicillosis

	CONFIRMED	**PROBABLE**
INFECTIONS (CONTINUED)		
PcP	A plus B: (A) compatible clinical syndrome, (B) microscopic or histological demonstration of *P. jirovecii* cysts in a pulmonary specimen	A plus B plus C plus D plus E: (A) dyspnea or cough, or fever progressive over > 1 week, (B) diffuse chest x-ray abnormality or, if on inhalational pentamidine, diffuse upper lung field abnormality, (C) evidence of hypoxia, (D) not suggestive of bacterial pneumonia (i.e., not purulent sputum or hemoptysis, no bacterial pathogen identified in blood or bronchial wash), (E) response to PcP treatment
Pneumocystis jirovecii, extrapulmonary	Compatible symptoms, plus microscopy	None
Pneumonia, recurrent bacterial, excludes: (a) post- obstructive pneumonias, including in those with intrapulmonary/bronchial lesions, (b) aspiration pneumonia, including in those with decreased consciousness levels, (c) nosocomial ventilator-associated pneumonias	Both pneumonia episodes must occur after enrollment and satisfy criteria (A) plus (B) plus (C). The recurrent pneumonia must also satisfy criteria (D) plus (E): (A) Signs and symptoms suggestive of bacterial pneumonia, (B) focal CXR abnormality compatible with bacterial pneumonia, (C) identification of a bacterial pathogen by positive blood culture, positive bronchoscopic sputum culture, detection of Legionella or pneumococcal antigen in urine or blood or diagnostic serologic findings, (D) the second pneumonia had onset of symptoms < 365 days after the first episode, (E) there is strong evidence that the first episode was cured such as an intervening clear CXR or absence of symptoms after > 1 month off antibacterials effective against pathogens commonly producing pneumonia	Both pneumonia episodes must occur after enrollment and satisfy criteria (A) plus (B). The recurrent pneumonia must also satisfy criteria (C) plus (D): (A) Signs and symptoms suggestive of bacterial pneumonia, (B) focal CXR abnormality compatible with bacterial pneumonia, (C) the second pneumonia had onset of symptoms < 365 days after the first episode, (D) there is strong evidence that the first episode was cured such as an intervening clear CXR or absence of symptoms after > 1 month off antibacterials effective against pathogens commonly producing pneumonia
PML (progressive multifocal leukoencephalopathy)	A or B: (A) positive histology, (B) compatible clinical and radiologic course and positive CSF PCR for JK virus	A plus B plus C: (A) Consistent symptoms, (B) brain image consistent with PML, (C) no response to toxo treatment or toxoplasma seronegative

	CONFIRMED	**PROBABLE**
INFECTIONS (CONTINUED)		
Rhodococcus equi disease	Clinical evidence of invasive infection plus microbiologic identification of the organism in the affected tissue or blood	None
Salmonella septicemia, recurrent	Both episodes must occur after enrollment and met criterion (A). The second episode must meet criteria (B) and C: (A) Positive blood or tissue culture, (B) the second septicemia had onset of symptoms < 365 days after the first episode, (C) the second septicemia must be due to a different Salmonella serotype or there must be strong evidence that the first episode was cured such as a negative blood culture off effective antibacterials for > 1 week or absence of symptoms off antibacterials for > 1 month	None
Toxoplasmosis of brain	Microscopy	A plus B plus C: (A) Symptoms of focal intracranial abnormality or decreased consciousness, (B) brain image consistent with lesion(s) enhanced by contrast, (C) positive toxoplasma serology or responds to treatment clinically or by scan
NEOPLASMS		
Cervical carcinoma, invasive	Histology (NOT carcinoma-in- situ)	None
Kaposi sarcoma, (mucocutaneous or visceral)	Histology	Highly typical appearance and persistence for > 1 month
Lymphoma, primary, of brain	Histology	Symptoms consistent with lymphoma plus at least one CNS lesion with mass effect plus lack of clinical and radiographic response to at least 2 weeks of treatment for toxoplasmosis
Lymphoma, Hodgkin's	Histology	None
Lymphoma, non-Hodgkin's, all cell types	Histology	None

	CONFIRMED	PROBABLE
NEUROLOGICAL		
HIV-related encephalopathy (including AIDS Dementia Complex)	None	Cognitive or motor dysfunction interfering with usual activity, progressive over weeks or months plus no other condition to explain the findings plus brain image obtained and suggests no other causes plus grade 2 or worse impairment in at least 2 domains by NARS (see below) excluding abnormal domains at trial entry. (For persons with abnormal domains at entry worsening by at least two grades meets criteria.)

Abbreviated NARS (Neuropsychiatric AIDS Rating Scale) Grading for HIV Encephalopathy

Adapted from: Price RW, Brew BJ. The AIDS dementia complex. J Infect Dis 1988; 158 (5): 1079- 83, and Hughes CP, Berg L, Danziger WL. A new clinical scale for the staging of dementia. Brit J Psych 1982; 140: 566-92.

NARS stage	Cognitive-Behavioral Domains					
	Orientation	**Memory**	**Motor**	**Behavior**	**Problem solving**	**Activities of daily living**
0.5	fully oriented	complains of memory problems	fully ambulatory slightly slowed movements	normal	has slight mental slowing	slight impairment in business dealings
1	fully oriented, may have brief periods of “spaciness"	mild memory problems	balance, co-ordination and handwriting difficulties	more irritable, labile or apathetic, withdrawn	difficulty planning and completing work	can do simple daily tasks, may need prompting
2	some disorientation	memory moderately impaired, new learning impaired	ambulatory but may require walking aid	some impulsivity or agitated behavior	severe impairment, poor social judgement, gets lost easily	needs assistance with ADLs
3	frequent disorientation	severe memory loss, only fragments of memory remain	ambulatory with assistance	may have organic psychosis	judgement very poor	cannot live independently
4	confused and disoriented	virtually no memory	bedridden	mute and unresponsive	no problem-solving ability	nearly vegetative

APPENDIX 6 – IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME GENERIC CRITERIA

(Revised 01/10/09)

From ACTG, available under https://actgnetwork.org/IRIS_Case_Definitions

1. **Initiation, reintroduction or change in antiretroviral therapy/regimen or therapy for opportunistic infections (OI).**

   AND

2. **[1]Evidence of:**

   a. **an increase in CD4+ cell count as defined by ≥50 cells/mm^3 or a ≥2- fold rise in CD4+ cell count, and/or**

   b. **decrease in the HIV-1 viral load of >0.5 log10 and/or**

   c. **weight gain or other investigator-defined signs of clinical improvement in response to initiation, reintroduction or change of either antiretroviral therapy/regimen or OI therapy.**

   AND

3. **Symptoms and/or signs that are consistent with an infectious or inflammatory condition.**

   AND

4. **These symptoms and/or signs cannot be explained by a newly acquired infection, the expected clinical course of a previously recognized infectious agent, or the side effects of medications.**
   AND

5. **For purposes of data collection, the infectious/inflammatory condition must be attributable to a specific pathogen or condition. A Clinical Events form should be completed 16 weeks (± 4 weeks) after initial report if diagnosis confirmed or changed from initial report**

[1] If the study participant is being evaluated for an inflammatory condition at a time that is <4 weeks after initiation, reintroduction or change in antiretroviral therapy/regimen or OI therapy, items 2a through 2c are not required.

Refer to the "Criteria for the Diagnosis of Specific Immune Reconstitution Inflammatory Syndromes (IRIS)" document for specific Opportunistic Infection (OI) and non-pathogen condition diagnosis criteria.

Criteria for the Diagnosis of Specific Immune Reconstitution Inflammatory Syndromes (IRIS)

IRIS Focus Group

Given the paucity of data for a clearly-defined immune reconstitution inflammatory syndrome for each opportunistic pathogen, the IRIS Working Group concentrated on developing specific definitions for the most well-characterized IRIS in the literature. IRIS events may occur as paradoxical worsening or as an unmasking. Paradoxical responses are described as an initial clinical worsening when patients are started on pathogen-specific therapy and/or ART simultaneously. Unmasking refers to aberrant clinical presentations of previously common OIs such as localized Mycobacterium avium *complex (MAC) lymphadenitis and* Cytomegalovirus *(CMV) vitritis occurring within the first weeks of starting ART suggesting that patients have sub-clinical disease prior to the initiation of ART. There are specific definitions including confirmed and probable for the following specific pathogen IRIS:* Mycobacterium avium *complex (MAC),* Progressive Multifocal Leukoencephalopathy *(PML),* Cytomegalovirus *(CMV),* Mycobacterium tuberculosis *(TB) and* Cryptococcus neoformans*. All other clinical syndromes attributed to immune reconstitution will be treated as probable IRIS events without specific definitions and will include* Pneumocystis jirovecii *pneumonia (PCP), Varicella Zoster (VZV), Herpes Simplex (HSV), Hepatitis B, Hepatitis C, Toxoplasmosis, Kaposi's Sarcoma, Graves' disease, Sarcoidosis, and other autoimmune disorders. For these less well-defined IRIS, key data will be captured on a generic form that includes clinical signs/symptoms, CD4, HIV RNA data, and clinical outcomes.*

Specific IRIS Case Definitions

1. ***Cytomegalovirus* (CMV): *{Ophthalmologic only}*** IRIS associated with CMV is fairly common; syndromes include uveitis, vitritis, extension or new development of retinal opacification, proliferative vitreoretinopathy (leading to retinal detachment), neovascularization, macular or optic nerve edema and subcapsular cataracts (leading to visual impairment) [1, 2]. The inflammatory component is marked, with significant anterior and/or posterior chamber inflammation. Vitritis and extension or new development of retinal opacification usually occurs within 3-12 weeks of beginning antiretroviral therapy/regimen and/or CMV antiviral therapy; uveitis may occur months to years after beginning antiretroviral therapy. Antiretroviral therapy/regimen is usually continued; some patients are also treated with anti-CMV drugs, especially those with sight-threatening disease. IRIS associated with gastrointestinal or neurologic (non-ocular) CMV disease have not be adequately characterized

   Confirmed CMV IRIS in patients *with* a prior history of CMV retinitis: previous CMV retinitis diagnosis by ACTG criteria and improvement of signs/symptoms with anti-CMV therapy, with the subsequent development of ocular inflammatory changes in uveovitreal tract, lens or retina, with or without associated visual changes, as documented by an experienced ophthalmologist.

   Confirmed CMV IRIS in patients *without* a prior history of CMV retinitis: the development of significant ocular inflammation in the uveovitreal tract, lens or retina attributed to CMV in the absence of ophthalmologic findings typical for acute CMV retinitis, with or without visual changes, as documented by an experienced ophthalmologist.

   Probable **CMV IRIS in patients *with* a prior history of CMV retinitis** previous CMV retinitis diagnosis by ACTG criteria and improvement of signs/symptoms with anti-CMV therapy, with the subsequent development of ocular inflammatory changes in uveovitreal tract, lens or retina, with or without associated visual changes, as documented by a non-ophthalmologist clinician

2. ***Cryptococcus neoformans***. The best described cases of *Cryptococcus neoformans* IRIS involve inflammatory changes developing in patients with recently diagnosed cryptococcal meningitis, cryptococcemia or pneumonia who have responded to appropriate antifungal therapy [1, 3,4]. Most have presented as meningitis, associated with CSF abnormalities (significantly elevated protein, lymphocytes, hypoglycorrhachia and cryptococcal antigen titers) with negative cultures. CNS imaging may demonstrate new meningeal inflammation. Significant elevations of intracranial pressure may occur. Non-CNS presentations are also common and have included the development of mediastinal or cervical adenopathy, necrotizing pneumonia, cavitation of previously documented pulmonary lesions, focal lymphadenitis and cutaneous abscesses. Biopsies may demonstrate granulomatous changes and cryptococci but typically cultures are negative. These presentations have occurred anywhere from two weeks to 11 months after initiation of antiretroviral therapy/regimen, with most cases occurring within three months. Less well described are cases of cryptococcal meningitis presenting only after initiation and response to antiretroviral therapy/regimen, also associated with elevated CSF cryptococcal antigen (CRAG) titers, negative CSF cultures and significant meningeal enhancement on scan.

   Confirmed cryptococcal IRIS in patients *with* a prior history of cryptococcosis: Cryptococcal meningitis or other diagnosis of systemic cryptococcal infection (fungemia, pneumonia) by ACTG criteria and improvement of signs/symptoms with antifungal therapy, with the subsequent development of new or worsening pulmonary infiltrates, new meningeal enhancement on scan or abnormal CSF findings (low glucose, elevated WBC, CSF CRAG with negative fungal culture), mediastinal or cervical lymphadenopathy, pleural effusion, cutaneous abscesses or cryptococcal lesions at other sites; histopathology from non-meningeal site demonstrating inflammatory changes and organisms in the absence of a positive culture or positive culture.

   Confirmed cryptococcal IRIS in patients *without* a prior history of cryptococcosis: the development of meningitis with meningeal enhancement on scan with abnormal CSF findings (low glucose, elevated WBC, positive CSF CRAG with negative or positive fungal culture), mediastinal or cervical lymphadenopathy, pleural effusion, cutaneous abscesses or cryptococcal lesions at other sites; histopathology from non-meningeal site demonstrating inflammatory changes and organisms in the absence of a positive culture or positive culture.

   Probable cryptococcal IRIS in patients* with *a prior diagnosis of cryptococcosis: *previous cryptococcosis diagnosis by ACTG criteria and improvement of signs/symptoms with anti-cryptococcal therapy, and the subsequent development of focal inflammatory site(s); histopathology from involved site or sterile body fluid analysis demonstrating inflammatory changes (e.g., granulomas, lymphocytes) in the absence of positive stains or cultures for any other pathogen or any non-infectious histopathologic diagnosis; and negative blood cultures for Cryptococcosis; and negative CSF CRAG if obtained or development of new onset CNS signs or symptoms with meningeal enhancement or other atypical radiographic changes with no evidence of other neurologic disease to explain the findings.*

   Probable cryptococcal IRIS in patients* without *a prior diagnosis of cryptococcosis: *the subsequent development of focal inflammatory site(s); histopathology from involved site or sterile body fluid analysis demonstrating inflammatory changes (e.g., granulomas, lymphocytes) accompanied by evidence consistent with cryptococcosis in the absence of positive cultures for any other pathogen.*

3. ***Mycobacterium avium* complex (MAC).** This is one of the best described IRIS. The most common presentation is focal lymphadenitis (especially cervical) with high fever, elevated WBC counts and negative blood cultures; fistula formation may occur. There is a significant inflammatory component on biopsy with necrotizing granulomas, caseation and AFB. The syndrome usually

occurs within 3-12 weeks of initiating antiretroviral therapy/regimen and/or anti-mycobacterial therapy**,** although rare cases have been described beyond 6 months with deep tissue foci, e.g. psoas abscess. MAC IRIS has presented as diffuse adenopathy, and as focal disease in diverse sites (paraspinous, mediastinal, abdominal, vertebral, pulmonary and CNS). [1,5,6]

Confirmed MAC IRIS in patients *with* a prior history of disseminated MAC (dMAC): previous disseminated MAC diagnosis by ACTG criteria and improvement of signs/symptoms with anti-MAC therapy, with the subsequent development of focal inflammatory site(s).

Confirmed MAC IRIS in patients *without* a prior history of dMAC: the development of focal inflammatory site(s); histopathology from the involved site demonstrating inflammatory changes (e.g., granulomas) accompanied by histologic or culture evidence of AFB consistent with MAC in the absence of positive cultures for any other AFB; and may have positive blood cultures for MAC.

Probable MAC IRIS in patients *with* a prior history of dMAC: previous dMAC diagnosis by ACTG criteria and improvement of signs/symptoms with anti-MAC therapy, and the subsequent development of focal inflammatory site(s); histopathology from involved site demonstrating inflammatory changes (e.g., granulomas) in the absence of positive stains or cultures for any other pathogen or any non-infectious histopathologic diagnosis; and negative blood cultures for MAC.

Probable MAC IRIS in patients *without* a prior diagnosis of MAC: the subsequent development of focal inflammatory site(s); histopathology from involved site demonstrating inflammatory changes (e.g., granulomas, lymphocytic infiltrates) and without evidence of any other specific pathogen (stains may be positive for AFB); and negative blood cultures for MAC.

4. ***Mycobacterium tuberculosis* (TB).** Tuberculosis-associated IRIS can present as one of two main syndromes: (1) a paradoxical reaction after the start of ART in patients receiving tuberculosis treatment ("paradoxical" tuberculosis-associated IRIS), or (2) a new presentation of tuberculosis that is "unmasked" in the weeks following initiation of ART with an exaggerated inflammatory clinical presentation or complicated by a paradoxical response ("unmasking" tuberculosis associated IRIS). A "paradoxical" response to anti-tuberculous therapy was described as far back as 1955 in patients initiating therapy. In the HAART era, IRIS associated with TB is common and occurs in approximately 8-43% and typically consists of new and persistent fever after starting antiretroviral therapy/regimen; worsening or emergence of intrathoracic adenopathy, pulmonary infiltrates or pleural effusions, *or* worsening or emergence of cervical nodes on serial exam or of other tuberculous lesions, such as skin and CNS. It usually occurs within the first 4 weeks of beginning antimycobacterial therapy with or without antiretroviral therapy/regimen but has been described as late as 9 months when the patient is smear-negative. Antiretroviral therapy/regimen can usually be continued, often with anti-inflammatory support; corticosteroids have been used in those with CNS lesions or who are critically ill [7-12].

   Confirmed TB IRIS in patients *with* a prior history of TB (paradoxical TB-associated IRIS): There are three components to this case-definition (adopted from Lancet Infect Dis 2008, reference 12):

   A) Antecedent requirements

   i) Diagnosis of tuberculosis: previous pulmonary (smear positive or smear-negative) or extrapulmonary TB diagnosis by ACTG criteria

AND

ii) Initial response with anti-TB therapy (i.e. stabilization or improvement of signs/symptoms with appropriate anti-TB therapy prior to initiation of ART)*. For example, there has been cessation or improvement of fevers, cough, night sweats).

* (Note: this does not apply to patients starting ART within 2 weeks of starting tuberculosis treatment since insufficient time may have elapsed for a clinical response to be reported)

(B) Clinical criteria

The onset of tuberculosis-associated IRIS manifestations should be within 3 months of ART initiation, re-initiation, or regimen change because of HIV treatment failure.

Of the following, at least one major criterion or two minor clinical criteria are required:

Major criteria

• New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement—e.g. tuberculous arthritis

• New or worsening radiological features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI)

• New or worsening CNS tuberculosis (meningitis or focal neurological deficit; e.g. caused by tuberculoma)

• New or worsening serositis (pleural effusion, ascites, or pericardial effusion)

Minor criteria

• New or worsening constitutional symptoms such as fever, night sweats, or weight loss

• New or worsening respiratory symptoms such as cough, dyspnea, or stridor

• New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) Alternative explanations for clinical deterioration must be excluded

• Failure of tuberculosis treatment because of tuberculosis drug resistance

• Poor adherence to tuberculosis treatment

• Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed)

• Drug toxicity or reaction

Confirmed TB IRIS in patients *without* a prior history of TB (ART "unmasking" TB-associated IRIS): Patient is not receiving treatment for TB when ART is initiated. Active TB is diagnosed after initiation of ART and the diagnosis of TB fulfils ACTG criteria for smear-positive pulmonary TB, smear-negative pulmonary TB or extrapulmonary TB. Active TB develops within 3 months of starting ART and one of the following criteria is met: heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component. For

example, presentations may include TB lymphadenitis or TB abscesses with prominent acute inflammatory features; the development of pulmonary* or extrapulmonary TB with no evidence of miliary disease accompanied by marked focal inflammation; or histopathology from involved site demonstrating inflammatory changes (e.g., granulomas, caseation) accompanied by histologic or culture evidence of AFB consistent with TB in the absence of positive cultures for any other AFB.

Probable TB IRIS in patients *with* a prior history of TB: "Probable" status should be assigned for cases where criteria A and B are met (see confirmed TB IRIS with a prior history of TB definition) but an alternative diagnosis or explanation for clinical deterioration cannot be fully excluded.

Probable TB IRIS in patients *without* a prior diagnosis of TB: Patient is not receiving treatment for TB when ART is initiated. Active TB is diagnosed after initiation of ART and the diagnosis of TB fulfils ACTG criteria for smear-positive pulmonary TB, smear-negative pulmonary TB or extrapulmonary TB. There is heightened intensity of clinical manifestations but there is not clear evidence of a marked inflammatory component to the presentation or the subsequent development of focal inflammatory site(s) is beyond 3 months of ART initiation.

5. ***Progressive Multifocal Leukoencephalopathy* (PML)**. Inflammatory responses to PML usually occur within 3 months of beginning antiretroviral therapy. Based on available data, the simultaneous diagnosis of PML and IRIS post-HAART initiation is more commonly observed (i.e. unmasking IRIS). Furthermore, it appears that paradoxical worsening PML IRIS is identified sooner (within 4 weeks) than unmasking PML IRIS. MRI with gadolinium shows contrast enhancement suggesting an inflammatory response, and biopsy reveals significant inflammation with gliosis, marked intraparenchymal and perivascular infiltration by macrophages and lymphocytic infiltrates (especially CD8 T cells), giant cells, with or without demyelination. Intense JC-specific PCR signals (or other immunoreactivity to papovavirus antigens) are detected in brain tissue even in the absence of positive JC CSF PCR. The clinical responses are mixed: some improve, and some have significant worsening with progression to death. A variable response to steroids has been described [1,13,14].

   Confirmed PML IRIS in patients *with* a prior history of PML: previous PML diagnosis by ACTG criteria (consistent CT or MRI scan with positive biopsy or positive CSF JC PCR and the absence of any alternative diagnosis), with the subsequent development of new or worsening CT or MRI findings with contrast enhancement; brain biopsy shows focal inflammatory changes accompanied by histologic or PCR evidence of PML in the absence of another diagnosis.

   Confirmed PML IRIS in patients *without* a prior diagnosis of PML: the development of new neurologic deficit(s) in patient with no previously recognized CNS infection or malignancy, accompanied by CT or MRI changes showing contrast enhancement; brain biopsy shows focal inflammatory changes accompanied by histologic or PCR evidence of PML in the absence of another diagnosis.

   Probable PML IRIS in patients *with* a prior history of PML: previous PML diagnosis by ACTG criteria (consistent CT or MRI scan with positive biopsy or CSF JC PCR and the absence of any alternative diagnosis), with the subsequent development of new or worsening CT or MRI findings with contrast in the absence of another diagnosis.

Probable PML IRIS in patients *without* a prior diagnosis of PML: the development of new neurologic deficit(s) in a patient with no previously recognized CNS infection or malignancy accompanied by CT or MRI changes showing contrast enhancement consistent with PML with no brain biopsy obtained. CSF findings cannot be attributable to another pathogen or disease process.

IRIS Diagnoses without Specific Case Definitions

Pathogen-Directed:

1. ***Kaposi's Sarcoma* (KS*).*** Rapid KS progression [15] and local swelling with adjacent lymphadenopathy [20] have both been reported as a manifestation of immune reconstitution after antiretroviral therapy/regimen initiation. Whereas the latter syndrome may truly represent an IRIS syndrome, if there is no clear evidence of any characteristic inflammatory component [1, 16], then the progression could be due to a failure to reconstitute KSHV-specific immune responses. KS-IRIS is defined as a sudden or more dramatic progression of disease than expected as part of natural history that occurs within 12 weeks of initiation of ART. ART alone should be continued for 4-6 weeks to monitor for clinical response. If the lesions stabilize, have a regression of inflammation or lesion number or size diminishes, this will be defined as IRIS. Should disease progression continue, then this is unlikely to be IRIS and should be defined as progression of disease and managed with appropriate KSHV specific therapies. The presence of inflammation on biopsy may assist in distinguishing progression of disease vs. IRIS.

2. **Hepatitis B and C.** *Significant increase in ALT over baseline (flares) have been documented after beginning antiretroviral therapy/regimen with HBV co-infection as well as after interruption of antiretroviral therapy/regimen (especially in patients with HBV on a 3TC- or tenofovir-containing regimen). After immune recovery HBV "flares" may occur if HBV is not being concomitantly treated, although there are other potential reasons to consider. These include:*

a) spontaneous HBeAg seroconversion;

b) treatment induced exacerbation of the underlying disease;

c) hepatotoxic effects of treatment;

d) withdrawal of active HBV drug;

e) development of resistance and return of replication, and/or

f) superimposed and unrelated acute liver disease (e.g. hepatitis A)

Liver biopsy may be helpful in determining evidence of drug related (eosinophilic infiltrate) vs. acute viral hepatitis (hepatocyte swelling with lobular inflammation).

Biopsy may also grade and stage chronic viral hepatitis. IRIS is less well-defined in HCV co-infection, and increases in liver enzymes on antiretroviral therapy/regimen may be multifactorial as well.

3. **Herpes simplex virus *(HSV).*** *The development of unusual presentations of HSV following the initiation of antiretroviral therapy/regimen attributed to immune reconstitution have been rarely described.*

Localized HSV vesicles may occur within 8 weeks of initiating ART among persons with no prior history and no new source contact to attribute it to. Symptoms and signs are frequently consistent with a primary infection. Chronic erosive or ulcerative lesions of the genitals have been described in individuals who had prior histories of genital HSV. The appearance and clinical course of the lesions attributed to immune reconstitution appeared inconsistent with these patients' previous HSV presentations. Proctitis has also been reported [1,18,19]. Routine viral cultures may or may not yield HSV though histochemistry studies may show evidence of HSV antigens in the absence of a positive viral culture. Histopathology in some cases may demonstrate an inflammatory infiltrate with unusual prominence of plasma cells and eosinophils. Response to antivirals appears to be variable.

4. ***Pneumocystis jirovecii pneumonia*** **(PCP).** Despite being the most common OI with a relatively high CD4 threshold for development, few clear cases of Pneumocystis pneumonia IRIS have been documented so far (likely because steroids have been established for the use of severe PCP). Cases have been described as worsening of pneumonia and even respiratory failure, although the patients reported received suboptimal courses of steroids [20]. To entertain a diagnosis of PCP IRIS, bronchoscopy should rule out an intercurrent pulmonary process.

5. **Syphilis*.*** *New reactive RPR within 12 weeks of starting ART in setting of known previously treated syphilis and documented nonreactive within past 2 years without new attributable source. May also present serologically as less than or equal to 4-fold change in titer in someone with previous history of treated syphilis and no new attributable source. May present with systemic symptoms including arthralgia. May improve with anti-inflammatories.*

6. ***Toxoplasmosis*****.** There is also a very small database for possible toxoplasmosis IRIS. No specific clinical pattern has been seen, and there is no clear evidence of an inflammatory component.

7. ***Varicella Zoster*** **(VZV).** The development of herpes zoster after initiation of antiretroviral therapy/regimen has been attributed to immune reconstitution. The incidence of zoster appears to be 2- to 5-fold greater in those receiving antiretroviral therapy/regimen compared to those not receiving antiretroviral therapy/regimen. Most cases occur in the first 16 weeks following initiation of antiretroviral therapy/regimen. Those with higher percentage of CD8+ lymphocytes at the time of initiation of HAART and at one month following antiretroviral therapy/regimen appeared to be at higher risk for zoster [21]. Most cases present as cutaneous dermatomal disease or mucocutaneous disease, are mild, occur without systemic symptoms and respond to antiviral therapy. Iritis and keratitis have been described rarely [1,22]. It is not clear that cutaneous zoster following initiation of antiretroviral therapy/regimen has a significant inflammatory component that differentiates this from routine VZV.

8. **Other viral dermatose**s. Eruptive onset of new common warts, flat warts, or epidermodysplasia verruciformis-type warts, or inflammation/rapid growth of previously stable cutaneous or genital warts, have been noted during immune restoration [23-24]. In addition, eruptive onset of new molluscum contagiosum or inflammation/enlargement of pre-existing mollusca during immune restoration has been described [25].

Non-Pathogen or Unknown Pathogen Directed

1. ***Autoimmune disorders*****.** Systemic lupus erythematosus, polymyositis, rheumatoid arthritis, relapsing polychondritis and Guillain-Barre have also been attributed to immune reconstitution following administration of antiretroviral therapy/regimen [1,26].

2. ***Follicular inflammatory eruptions***. Sudden onset of follicular papulopustular inflammatory eruptions resembling acne vulgaris or acne rosacea have been reported within first 4 months of immune reconstitution [27]. Eosinophilic folliculitis, distinguished from acneiform eruptions by intense pruritus, an urticarial appearance to the papules, and histopathology showing follicular inflammation containing eosinophils, has been documented. An increased incidence of eosinophilic folliculitis has been noted in the first 6 months of HAART therapy [28].

3. ***Graves' Disease***. New onset of clinically significant Graves' disease (hyperthyroidism) has been reported following the initiation of antiretroviral therapy/regimen. The development of anti-thyrotropin receptor antibodies in individuals following antiretroviral therapy/regimen, not present before antiretroviral therapy/regimen initiation has been described [1, 26].

4. **Sarcoidosis.** *Worsening of previously diagnosed sarcoidosis or newly diagnosed sarcoidosis following antiretroviral therapy/regimen has been reported. Pulmonary involvement as well as extrapulmonary involvement (erythema nodosum) has been described [1, 26].*

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APPENDIX 7 – HIGHLY EFFECTIVE METHODS FOR AVOIDING PREGNANCY IN FEMALES OF CHILD BEARING POTENTIAL*

The following is the all-inclusive list of the highly effective methods for avoiding pregnancy (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).

The list does not apply to females of childbearing potential (FCBP) with same sex partners, when this is their preferred and usual lifestyle.

- True abstinence from penile-vaginal intercourse, when this is in line with the preferred and usual lifestyle of the subject [Hatcher, 2007a] (Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception].
- Non-hormonal Intrauterine device or non-hormonal intrauterine system that meets the effectiveness criteria as stated in the product label [Hatcher, 2007a]
- Male partner sterilization prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007a]. The information on the male sterility can come from the site personnel's: review of subject's medical records; medical examination of the subject and/or semen analysis; or interview with the subject on his medical history.
- Combined (oestrogen and progesterone containing) hormonal contraception associated with the inhibition of ovulation***:
    - Oral
    - Intravaginal
    - Transdermal
- Bilateral tubal occlusion

* A Woman of childbearing potential (WOCBP) is defined as any female who has:

- Experienced menarche
- Not undergone surgical sterilization (hysterectomy , bilateral salpingectomy or bilateral oophorectomy)
- Not experienced menopause. Women are considered menopausal if they have not had a menses for at least 12 months and have an FSH (follicle stimulating hormone) of greater than 40 IU/L or, if FSH testing is not available, they have had amenorrhea for 24 consecutive months**.

**Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level.

***If a patient is randomised to Symtuza, an alternative highly effective method of contraception should be used

APPENDIX 8 – SAFETY REPORTING FLOW CHART

Safety Data	Reporting Format	Timelines
All SAEs arising during the Clinical Trial, regardless of Investigator/designee causality assessments against IMP(s)	SAE form	Site to report to sponsor within 24 hours of first becoming aware of the event. Sponsor to report to Funder within 24 hours of awareness.
Pregnancy information for all female Clinical Trial Subjects who become pregnant while participating in the Clinical Trial and following exposure to an IMP. The subject will also be followed to determine the outcome of the pregnancy (including information on the status of the mother and child), which will also be reported to sponsor.	Copies of the original Pregnancy CRF pages	Site to send to sponsor within 24 hours of first becoming aware of the pregnancy or the pregnancy outcome. Sponsor to report to Funder within 24 hours of awareness.
Deaths	Any AE, AR or unexpected AR that results in death should be reported as an SAE on an SAE form.	Site to report to sponsor within 24 hours of first becoming aware of the event. Sponsor to report to Funder within 24 hours of awareness.
Overdose	If the overdose fits the criteria of an SAE (see Section 8) it should be reported appropriately on an SAE form, else report as a Special Reporting Situation.	Site to report to sponsor within 24 hours of first becoming aware of the event. Sponsor to report to Funder within 24 hours of awareness.
Special Reporting Situations: (See section 8.10)	Email	Site to report to sponsor within 24 hours of first becoming aware of the event. Sponsor to report to Funder within 24 hours of awareness.
Product Quality Complaints	Email	Site to report to sponsor within 24 hours of first becoming aware of the event. Sponsor to report to Funder within 24 hours of awareness.

APPENDIX 9 – AMENDMENT HISTORY

Comparative table with Description of Change and Rationale for change to the Protocol from Version 2.0 to Version 4.0.

Please note version 3.0 was never fully approved in any territory as it did not include changes approved between versions 1.5 and version 2.0. V4.0 re-incorporates all approved changes made previously and also includes the following:

Change No.	Description of Change	Rationale for Change
1.	Changes made to reference the compliance with Clinical Trial Regulation (EU) No 536/2014 in the statements the CI, Sponsor, statistician, and PIs sign. Addition of EUCT number to title page.	Compliance with Clinical Trial Regulation (EU) No 536/2014
2.	Protocol summary: Number of sites and countries changed from 45 to 61, and 7 to 11, respectively.	Expansion of trial sites and territories is ongoing.
3.	Section 1.2.1: Therefore, in cases when needs *ART needs* to be initiated before genotypic testing results are available	Typographical error on in the background and rationale section
4.	Section 1.2.1, Section 7.1 and Section 7.7: Change to the language regarding the referenced RSI provided by the sponsor in	Changed to emphasize that the study team should refer to the particular SmPC provided and authorised as the RSI in the study, even if this is not the local country version or most current.
5.	Section 5.2: Exclusion Criteria: Removal of the requirement that forbidden concomitant medications should have been stopped at least 30 days ahead of baseline.	30 days was added initially at the start of the trial when there was less safety data available for Biktarvy, in particular, as it was not yet authorised when the protocol was written. Therefore, it was thought to exclude all contraindicated medication for 30 days as a safety precaution. However, it is now thought this is unnecessary and the sites should follow any recommendations in the SmPC.
6.	Section 5.2 and Appendix 1: A latent TB test may be performed. Previously a TB test will be performed	To clarify that the test is to confirm if latent TB is present. Additionally, TB testing has always been intended to be done in those patients in who it may be suspected. This wording has been changed to clarify that.
7.	Removal of “Investigator Brochure” from the title of section 7.1	There is no Investigator Brochure used for the trial.
8.	Section 8.2.4 and Section 8.3.3.:	Addition in line with change to Sponsor’s safety event reporting form

Change No.	Description of Change	Rationale for Change
	1. Additional text to state that details of reporter included on the Safety Event Report Form 2. Addition of text to mention the pharmacovigilance management plan (PVMP) will be used by the CI and sponsor in assessment of safety reporting	to include the pharmacovigilance management plan (PVMP).
9.	Section 8.2.4 Recording and Reporting of SAEs and SUSARs Statement made that the Sponsor will update the Eudrvigilance database.	Compliance with Clinical Trial Regulation (EU) No 536/2014
10.	Section 8.3.6 and Section 12 Addition of details regarding Endpoint committee review	An endpoint committee may be requested ahead of any data analysis required by the DSMB or the TSC.
11.	8.8 Development Safety Update Reports Statement of intent for the sponsor to submit a single safety report for both IMP	Compliance with Clinical Trial Regulation (EU) No 536/2014
12.	9.5 Interim analysis and criteria for the premature termination of the trial Statement that there are no specific trial stopping criteria	Compliance with Clinical Trial Regulation (EU) No 536/2014
13.	13.3 Regulatory Compliance Change to reflect the trial will be conduct in compliance with Clinical Trial Regulation (EU) No 536/2014	Compliance with Clinical Trial Regulation (EU) No 536/2014
14.	13.6 Data protection and patient confidentiality Updated to comply with the Clinical Trial Regulation (EU) No 536/2014	Compliance with Clinical Trial Regulation (EU) No 536/2014
15.	Section 13.5: Change to the definition of serious breach and reporting timelines	The previously included strictly MHRA definition has hence been modified to include the Clinical Trial Regulation wording.
16.	Appendix 1: Study Flowchart Removal of “including urinary chemistry” after “Clinical Chemistry” in the description of this assessment	The words are superfluous as the actual tests required are described in the footnote 12 – removing them for clarity for the sites.
17.	Appendix 1: Change to the footnote 10 wording after the asterisk: regarding when assessments should be taken. Changing from “after baseline” to “at all visits required”	Changing this for clarity as it is ambiguous about whether urinalysis assessments should be done at all visits.
18.	Appendix 1: Additional wording to state that either urinary creatinine or ACR and PCR are mandatory, not both	As it is the ACR and PCR which are required, and these are calculated from the urinary creatinine, if the ACR and PCR are provided by the site directly and the site do not routinely

Change No.	Description of Change	Rationale for Change
		also provide the urinary creatinine in lab reports, this is acceptable.
19.	Appendix 1: Change to clarify that, as CD4 and CD8 can be calculated from total lymphocytes and CD4% and CD8%, CD4 and CD8 count are not mandatory	CD4% and CD8% and lymphocytes are already mandatory.
20.	Appendix 1: Urinary nitrites are no longer mandatory	It is considered that urinary nitrites are not a necessary safety test that is needed.

Comparative table with Description of Change and Rationale for change to the Protocol from Version 4.0 to Version 5.0.

Change No.	Description of Change	Rationale for Change
1.	Section 13.6: Additional wording to clarify how data is stored and processed at the end of the study, and in what format	Compliance with Clinical Trial Regulation (EU) No 536/2014

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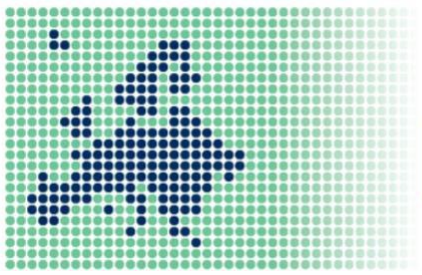

neatid

The European treatment network for HIV, hepatitis and global infectious diseases

STATISTICAL ANALYSIS PLAN

TRIAL FULL TITLE	An Open-Label, Multi-Centre, Randomized Study to Investigate Integrase Inhibitor Versus Boosted Protease Inhibitor Antiretroviral Therapy for Patients with Advanced HIV Disease
Short Title/Acronym	LAPTOP -The Late Presenter Treatment Optimization Study -
Clinical Phase	3
EUDRACT NUMBER	2018-003481-13
Clinitrials.gov identifier	NCT03696160
SAP VERSION	0.3
SAP VERSION DATE	22.11.2023
SAP AUTHOR	Lambert ASSOUMOU

SIGNATURES

Responsibility	**Name**	**Signature**	**Date**
Trial statistician	Lambert ASSOUMOU		
Chief Investigator	Georg BEHRENS		
Sponsor	Anton POZNIAK		

DOCUMENT HISTORY

Document version number	Section change	Summary of changes	Reason for change

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

Acronym	Description
3TC	Lamivudine
ABC	Abacavir
ACTG	AIDS Clinical Trial Group
ADE	Adverse Drug Event
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
ANRS	Agence Nationale de Recherches sur le SIDA (National Agency for AIDS Research)
AST	Aspartate Aminotransferase
B/BIC	Bictegravir
BI	Bacterial Infection
C	Cobicistat
CDC	Centres for Disease Control and Prevention
CI	Chief Investigator
CI	Confidence Interval
CRF	Case Report Form
SAP	Statistical Analysis Plan
D/DRV	Darunavir
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DTG	Dolutegravir
EACS	European AIDS Clinical Society
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ELISPOT	Enzyme-Linked ImmunoSpot
ETV	Early Termination Visit
EU	European Union
EudraCT	European Clinical Trials Database
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FTC/F	Emtricitabine
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type-1
IAS	International AIDS Society
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IGRA	Interferon-Gamma Release Assays
IMP	Investigational Medicinal Product
INI	Integrase Inhibitor

INSTI	Integrase Strand Transfer Inhibitor
IRIS	Immune Reconstitution Inflammatory Syndrome
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NNRTI	Non-Nucleoside Reverse-Transcriptase Inhibitor
NRTI	Nucleoside Reverse-Transcriptase Inhibitor
OI	Opportunistic Infection
PI	Protease Inhibitor
QD	quaque die (once daily)
QOL	Quality of Life
RAL	Raltegravir
RNA	Ribonucleic Acid
RT	Reverse Transcriptase
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	Tenofovir Alafenamide Fumarate
TDF	Tenofovir Disoproxil Fumarate
TB	Tuberculosis
TFV	Tenofovir
US	United States

1. INTRODUCTION

1.1 PREFACE

The effectiveness of HIV antiretroviral therapy (ART) has consistently improved over the years. This is due to novel compounds and combinations with improved antiviral efficacy and side effect profiles resulting in less virologic failures and treatment discontinuation. On the other hand, most recent randomised controlled trials for first line treatment consider patients with less advanced disease (mean CD4 cell counts at baseline >350/µl, less than 15% of patients with CD4 cell counts <200/µl) and low baseline viral loads (DeJesus *et al.*, 2012) (Raffi *et al.*, 2013) (Walmsley *et al.*, 2013) (P.E. Sax *et al.*, 2017) (Gallant *et al.*, 2017). This favours superior overall response rates, as these patients usually suffer from less co-morbidity, drug-drug interactions (DDI), and other risks for treatment failure. The rate of patients with acquired immunodeficiency syndrome (AIDS) recruited into these trials was low, while a third of HIV-positive patients are diagnosed late in the course of the disease (CD4 T-cell count <200 cells/L or presence of AIDS) (Raffetti *et al.*, 2016) (Sobrino-Vegas *et al.*, 2012). Much less is known about which ART regimens perform best in late presenters in terms of viral efficacy, immune reconstitution, improvement of AIDS-related co-morbidities and adverse events (AEs). No specific combinations have been compared in sufficiently powered randomised clinical trials, and all regimens considered in international guidelines for first line therapies are judged as equal standard of care for these patients. Initially, protease inhibitor (PI) containing regimens were frequently used in patients presenting late or with AIDS defining events (Mussini *et al.*, 2008).

However, specifically regimens containing integrase inhibitors (INI) are promising candidates for treatment combinations in patients with CD4 cell counts <200/µl due to their antiviral activity and rapid decline of viral load, beneficial side-effect profile and metabolism pathways compared to other regimens. Also, integrase inhibitors such as dolutegravir (DTG) and bictegravir (BIC/B) have high genetic barriers, thereby preventing resistance mutation development and ensuring sufficient antiviral activity in case of pre-existing mutations against nucleosides (Demarest *et al.*, 2018). Therefore, in cases when needs ART to be initiated before genotypic testing results are available, current European AIDS Clinical Society (EACS) Guidelines (EACS Treatment Guidelines 9.0) recommend to include a drug with a high genetic barrier to resistance in the first-line regimen (e.g. PI or DTG).

We therefore propose a strategic clinical trial to compare an INI containing regimen versus a boosted PI regimen in patients with advanced HIV-infection. We aimed to demonstrate the non-inferiority of an INI containing regimen [bictegravir (B) /emtricitabine (F) /tenofovir alafenamide (TAF) QD] versus a boosted PI regimen [darunavir (D) /cobicistat(C) /emtricitabine (F) /tenofovir alafenamide (TAF) QD] in patients with advanced HIV infection. The superiority of the INI-based treatment group over the PI-based treatment group will be assessed in the event that non-inferiority is established.

This Statistical Analysis Plan (SAP) details the different populations of analysis and the statistical methodology that will be used to analyse the data. It describes the efficacy and safety variables and anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol. The analyses described are based upon the clinical study protocol Version 2.0 dated 16 June 2020. This SAP will be validated and signed before the primary endpoint analysis is performed.

1.2 PURPOSE OF THE ANALYSES

The main purpose of this analysis is to compare two different types of HIV treatments, in terms of effectiveness and improvement of side effects, for patients who are diagnosed with a more advanced HIV infection. Patients with advanced HIV infections are otherwise known as 'late presenters'. These analyses will assess the efficacy and safety of BIC containing regimen in comparison with the boosted PI containing regimen. Advanced HIV infection is defined by an AIDS-Defining-Events (ADE) and/or an absolute number of T CD4+ lymphocytes ≤ 200/mm^3.

The statistical analyses of the primary and secondary endpoints will be performed after the database locked and cleaned. The analysis will include all randomised patients enrolled who received at least one dose of the study drugs.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 Primary objective

The primary objective of this study is to demonstrate the non-inferiority of an INI containing regimen [bictegravir (B)/**emtricitabine(F)/tenofovir alafenamide (TAF)** QD] versus a boosted PI regimen [darunavir (D)/cobicistat (C)/**emtricitabine (F)/tenofovir alafenamide (TAF)** QD] in patients with advanced HIV infection, in terms of reducing the occurrence of a composite outcome including virological and clinical reasons.

2.1.2 Secondary objectives

The secondary objective of this study is to investigate the immunological and virologic response, tolerability, resistance development, discontinuation of therapy due to tolerability, quality of life (QoL) and IRIS incidence.

2.1.3 Exploratory objectives

The exploratory objective of this study is to assess whether virologic response is better predicted by deep sequencing rather than standard population sequencing.

2.2 ENDPOINTS

2.2.1 Primary endpoint/outcome

The primary endpoint is time to failure. Failure is defined as the first occurrence of any of the following components:

1. Virologic reasons
    a) Insufficient virologic response, either:
        a. HIV-1 RNA reduction < 1 log 10 copies/mL at week 12, or
        b. Viral load > 50 HIV-1 RNA copies/mL at week 48
    b) Viral rebound, which is subsequently confirmed at the following scheduled or unscheduled visit, defined as either:
        a. Rebound of HIV-1 RNA to >200 copies/mL after having achieved HIV-1 RNA <50 copies/mL
        b. Rebound of HIV RNA by >1 log 10 copies/mL from nadir value, for patients whose viral load has never been suppressed below 50 copies/mL
2. Clinical reasons
    a) Death related to HIV, AIDS, OI/severe BI or complications of therapy including IRIS
    b) Any new or recurrent AIDS defining event on, or after 28 days of therapy
    c) Any new serious non-AIDS defining event documented by the endpoint review committee (including severe BI, end stage liver disease, renal failure, cardiovascular event, and non-AIDS related malignant disease)
    d) Clinically relevant AEs of any grade or IRIS which require treatment interruption (lasting > 5 days) of INI or boosted PI therapy within the first 48 weeks after randomisation
    Note: Discontinuation of BIC or boosted DRV followed by (within 5 days) continuation with another INI or PI, respectively, is not considered as a strategy failure or endpoint.

All clinical events will be validated as endpoints by the Clinical Endpoint Committee.
Clinical events are referenced in the appendices : Appendices 1 (AIDS-Defining Conditions), 2 (INSIGHT Serious Non-AIDS Events Criteria), 3 (INSIGHT Progression of HIV Disease Criteria) and 4 (Immune Reconstitution Inflammatory Syndrome Generic Criteria).

2.2.2 Secondary endpoints/outcomes

Secondary endpoints/outcomes included:

- Cumulative incidence of the composite primary endpoint at week 48
- Proportion of patients with HIV-RNA viral load <50 copies/mL at week 24, 36, 48
- HIV-1 drug resistance at confirmed virological failure [Time Frame: Through study completion, an average of 1 year]
- Time to reach CD4 count >200/µL (first measurement)
- Proportion of patients with CD4 cell count < 200 µL and < 350µL at week 4, 8, 12, 24, 36, 48
- CD4/CD8 ratio at week 4, 8, 12, 24, 36, 48
- Incidence of IRIS in the two arms through week 48
- Incidence and duration of hospitalisation or rate of relapse of specific opportunistic infection (OI) or bacterial infection (BI) through week 48
- Number and proportion of participants with Grade 2, 3 and 4 adverse events (AEs), treatment-related AEs, AEs leading to the study drug discontinuation, and death through week 48
- ART and OI/BI treatment changes and dose modifications due to toxicities and DDI with ART, and IRIS through week 48
- Healthcare resource use, including total inpatient days and emergency room visits through week 48
- QOL and functional status outcomes, including overall self-reported QOL and functional status compared in the two groups at week 48
- Discontinuation or modification of study medication due to insufficient virological response, resistance mutations at baseline, or resistance mutation development before week 48

2.2.3 Exploratory endpoints/outcomes

- Mutations detected by deep sequencing compared with those detected by population sequencing
- Proportion of patients with HIV-RNA viral load < 50 copies/mL at week 4, 8, 12

3. STUDY METHODS

3.1 GENERAL STUDY DESIGN AND PLAN

LAPTOP study is an international, open-label, randomised, two arm, multicentre trial over 48 weeks to compare two strategies for HIV-1 infected patients with advanced disease.

Eligible patients will be randomised to receive either an integrated inhibitor containing regimen (B (50mg)/F (200mg)/TAF (25mg) [1 pill administered orally once daily for 48 weeks]) or a boosted PI regimen (D (800mg)/C (150mg)/F(200mg)/TAF (10mg) [1 pill administered orally once daily for 48 weeks]). Randomisation is stratified by country and baseline CD4 cell count (<50 cells/µL, 50-199 cells/µL, or ≥200 cells/µL).

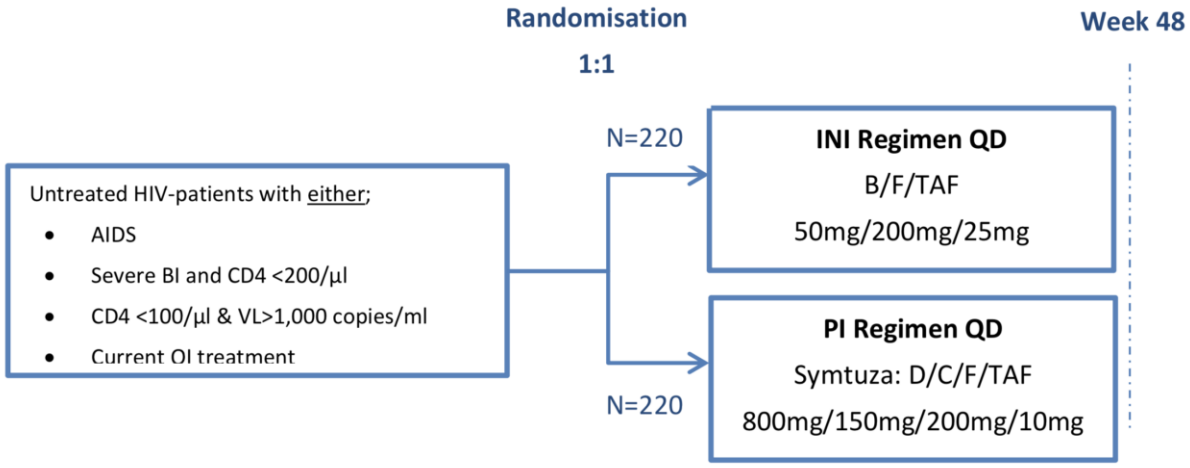

Figure 1: Study design

Study participants will be ART-naïve, HIV-1-infected individuals aged 18 or older who have at entry HIV viral load > 1000 copies/ml and at least one of the following: i) have AIDS with any CD4 cell count; ii) have severe bacterial infection (BI) and must have a CD4 cell count < 200/µl within 30 days prior to study entry; iii) are asymptomatic with CD4 cell count < 100/µL within 30 days prior to study entry; iv) are currently receiving treatment for OI. Women who were pregnant or breastfeeding or who declined a contraceptive method at screening were not eligible.

After the screening visit, participants will be seen at baseline, when they initiated c-ART and weeks 4, 8, 12, 24, 36 and 48, as well as a follow-up visit 30 days following the week 48 visit.

At each visit, participants will have routine safety monitoring as well as measurement of plasma HIV-1 RNA viral load, CD4, CD8 cells counts and a deep sequence resistance test. In the event of virological failure, local resistance tests should be performed on the first sample, and participants should discontinue study treatment and receive rescue therapy at the investigators' discretion. Quality of life (QoL) questionnaire (EuroQoL EQ-5D-3L) and HIV Symptom Index (HIV-SI/SDM) questionnaire will be administrated at each visit from baseline.

3.2 Randomisation Scheme and Blinding

The randomization list will be generated by an independent statistician not part of the study team. The list will be generated by a centralized computer-generated random list with a permuted block size. He is the only person who know the size of the blocks.

Participants will be randomly assigned, in a 1:1 ratio, to receive a BIC containing regimen or boosted PI containing regimen for 48 weeks, with allocation stratified by country and baseline CD4 cell count (<50 cells/µL, 50-199 cells/µL, or ≥200 cells/µL).

Randomization will be done at the baseline visit (date of the study treatment initiation). This study is open-label; therefore, all investigators, site pharmacists, study nurses and participants will be unmasked and aware of the treatment allocation throughout the study.

3.3 STUDY SCHEDULE

Procedure	**Screening Visit**	**Baseline Visit2**	**Treatment Phase**						**Follow Up/Early Termination Visit**
	Day -28 to Enrolment[1]		**Week 4 (± 7 days)**	**Week 8 (± 7 days)**	**Week 12 (± 7 days)**	**Week 24 (± 7 days)**	**Week 36 (± 7 days)**	**Week 48 (± 7 days)**	**30 days following Week 48 visit (± 7 days)**
Informed consent	X								
Eligibility assessment[3]	X								
Demographics	X								
Medical and social history[4]	X								
ECG[5]	X								
HBV and HCV testing[6]	X								
TB test[7]	X								
Local Resistance testing[8]	X								X
Randomisation		X							
Symptom-directed physical examination		X	X	X	X	X	X	X	X
Vital signs[9]	X	X	X	X	X	X	X	X	X
Urinalysis[10]		X			X	X	X	X	X
Haematology (including CD4 & CD8 testing)[11]	X	X	X	X	X	X	X	X	X
Clinical chemistry[12] (including urinary chemistry)	X	X	X	X	X	X	X	X	X
Viral load testing[13]	X	X	X	X	X	X	X	X	X
Sample collection for central resistance testing (deep sequencing)[14]		X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse event assessments		X	X	X	X	X	X	X	X
Quality of Life questionnaire (EuroQoL EQ-5D-3L)		X	X	X	X	X	X	X	X
HIV Symptom Index questionnaire (HIV-SI/SDM)		X	X	X	X	X	X	X	X
Dispensing of trial drugs[15]		X			X	X	X		
Adherence[16]					X	X	X	X	
Serum pregnancy test[17]	X								
Urine pregnancy test[18]		X	X	X	X	X	X	X	X
Physical examination (including height & weight)[19]	X	X	X	X	X	X	X	X	

	Assessment sub notes	Parameters/Notes
1	Screening visit	The maximum time between screening visit and baseline visit is 28 days; however, participants should be invited for their baseline visit as soon as reasonably possible in order to start their treatment. Only the following laboratory assessments are required for screening and historic (up to 28 days old) tests results may be used for screening: • HBV and HCV testing • TB test • CD4 & CD8 testing • Platelet count testing • Clinical chemistry (only creatinine, creatinine clearance, eGFR, potassium, sodium, ALT, AST is required) • Viral load testing • Resistance testing (the last resistance test carried out can be used) A serum pregnancy test is mandatory at the screening visit for women of child bearing potential
2	Baseline visit	For baseline results, all screening tests carried out within 10 days before baseline can be used. This includes historic screening results, as long as they fall within the 10 day window before baseline. Screening data obtained more than 10 days from baseline, must be repeated at baseline.
3	Eligibility	According to the inclusion/exclusion criteria.
4	Medical & social history	Including: • Recreational drug use • Smoking history • Alcohol intake • Concomitant diseases • Past & present medical history, including HIV- associated conditions • Review of any medication taken within the last 30 days
5	ECG	12-Lead ECG performed supine. If an ECG is not performed at screening, it must be performed by the time of the baseline visit.
6	HBV & HCV testing	HBV antigen test and hepatitis C (HCV) antibodies test (if patient tests positive for HCV antibodies, test for HCV RNA, if positive and chronic for either HBV or HCV, add HBV DNA test at baseline visit). HBV test to be repeated in event of positive result. Participants with active HBV infection at study entry will be monitored throughout the study and additional HBV DNA tests performed at the Week 24 and 48 visits. For screening, test results 28 days prior to the screening visit can be used
7	TB Testing	A TB test (IGRAs e.g. ELISPOT, QuantiFERON) will be performed in patients with expected latent TB at the screening visit. For screening, test results 28 days prior to the screening visit can be used. Patients can be randomised into the study without having the latent TB screening results available at randomisation A TB test can be performed at subsequent visits on the basis of clinical suspicion.
8	Resistance testing (performed locally)	A local resistance test will be performed at the screening visit. This result is not required for eligibility or prior to randomisation. If a HIV resistance test was done previously and results are available, the last resistance test carried out shall be considered. An additional resistance test will be performed at the ETV for patients with virological failure or insufficient virological response.
9	Vital Signs (10 mins resting)	Including: • Pulse • Blood pressure
10	Urinalysis	Including: • Urinary creatinine* • Urinary glucose (dipstick test sufficient)* • Urinary proteins* • Albumin (can be obtained from 'spot' urine test) • Nitrites (dipstick test sufficient) * • Albumin: Creatinine Ratio (ACR) and Protein: Creatinine Ratio (PCR) • Urinary phosphate • Beta-2 microglobulin • Leukocytes (dipstick test sufficient)

		* Assessments should be performed as per local site procedure; however, assessments marked with an asterisk are mandatory for the study at and after baseline.
11	Haematology (non-fasting)	Including: • Platelet count* • RBC Count (indices MCV & MCH)* • WBC count (absolute)* • CD4 Count and %* • CD8 Count and %* • Haemoglobin* • Haematocrit*
		RBC Count indices: • MCV • MCH Automated WBC differentials: • Neutrophils* • Lymphocytes* • Monocytes • Eosinophils • Basophils
		* Assessments should be performed as per local site procedure; however, assessments marked with an asterisk are mandatory for
		the study.
		Assessments that have been underlined are required at screening (results up to 28 days old can be used).
12	Clinical chemistry (non-fasting)	• Urea* • Chloride* • Alkaline phosphatase* • Creatine phosphokinase* • Creatinine* • Calcium* • Phosphate* • Creatinine clearance, eGFR* (Calculations: Cockcroft-Gault (requires weight), MDRD, CX-Epi) • Glucose* • Total* and indirect bilirubin • Potassium* • Total protein* • Sodium* • ALT* • AST* • Albumin* • Cholesterol* • HDL* • LDL* • Triglycerides*
		* Assessments should be performed as per local site procedure; however, assessments marked with an asterisk are mandatory for the study at
		and after baseline.
		Assessments that have been underlined are required at screening (results up to 28 days old can be used).
13	Viral load testing	HIV RNA viral load-results obtained 28 days prior to screening can be used.

14	Resistance testing for deep sequencing (sent to central laboratory)	In addition to the resistance test performed locally, a resistance testing sample will be taken at the Baseline visit, each visit in the treatment phase (Week 4, 8, 12, 24, 36 and 48) and at the ETV (for patients with virological failure identified outside of a scheduled visit). All resistance testing samples for patients with virological failure will be sent to a central laboratory for next generation sequencing to look for low-level pre-existing resistance in cases of suspected resistance development.
15	Drug dispensing	There will be four dispensations of the study medication to the patient (Baseline visit, Week 12, 24 and 36).
16	Adherence	Also performed at the ETV if required.
17	Serum pregnancy test	For women of child bearing potential only (see Appendix 7 for definition).
18	Urine pregnancy test	Dipstick and urine pregnancy test (WOCBP only - see Appendix 7 for definition). This is a mandatory assessment. If a urine pregnancy test is not possible, a serum pregnancy test can replace this.
19	Physical examination	Weight is required at all visits, as detailed in the appendix 1, however height is only required at baseline.

4. SAMPLE SIZE CALCULATION

In the ANRS 146 OPTIMAL trial [Levy et al.], of late presenters, the proportion of patients with severe morbidity (new adverse drug event (ADE), other HIV related diseases, serious non-AIDS events, IRIS and death) was estimated at 12.2% per year in the boosted PI arm. The virological failure was estimated at 20% at week 48 in the DRV/r group of the IMEA 040 DATA study (Slama L et al) that recruited a similar population. As a few subjects will meet more than one of these criteria, we assumed a cumulative probability of failure at 25% at 48 weeks in the PI regimen group.

A total of 404 evaluable subjects, randomized in a 1:1 ratio to 2 treatment groups (202 subjects per treatment group), achieves at least 80% power to detect a non-inferiority margin of 1.606 in the hazard ratio, which corresponds to a 12% difference in the cumulative probability of failure rate between INI-based regimen group (37%) and PI-based regimen group (25%), with 97 events required. The sample size and power calculation assume that the cumulative probability of failure is 25% for the PI regimen group and 23% for the INI-based regimen group (i.e. the expected hazard ratio is 0.909), using a non-inferiority margin of 1.606 in hazard ratio and a two-sided 95% confidence interval (CI). The sample size and power calculation were made using the statistical software package nQuery Advanced, non-inferiority testing of two survival curves using cox regression module (Version 8.1.2.0).

With an estimated ~7.5% drop off rate/year, we plan to enrol 220 subjects per group to ensure we have sufficient power for this per-protocol analysis.

Superiority of INI-based regimen group versus PI-based regimen group will be evaluated after the non-inferiority is established. With an ITT analysis, 440 subjects and 78 events, a two-sided log-rank test at an alpha level of 0.05 will achieve at least 80% power to detect a 50% reduction in hazard rate in INI-based regimen (i.e. the hazard ratio is 0.5). A 50% reduction in hazard rate means that INI-based regimen could decrease the risk by 11.6% (25% for PI- vs 13.4% for INI- based regimen).

5. GENERAL CONSIDERATIONS

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation (SD), 1st quartile, median, 3rd quartile, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical variables.

The number of participants and the flowchart of the study will be presented. The period of enrolment and the total number of participants screened to be included in the study will be presented. The number of ineligible participants and the total number of randomized participants will be presented.

The number of participants who never receive the study intervention will also be presented by treatment group and those who were included in the full analysis set and the safety analysis set will be presented.

Baseline is considered as the day 1 visit and the baseline data is data collected just before intervention at day 1.

5.1 TIMING OF ANALYSES

Before the final analysis is performed, the trial Statistician will write the statistical code needed to perform the statistical analyses required by the SAP. A temporary version of the trial database should be sent to the Trial Statistician for final SAP and code preparation. The code together with the temporary version of the trial database will result in a mock-up report. The Trial Statistician will review the mock-up report, and subsequently the SAP will be updated if needed before the final version is approved and signed-off. The final analysis will be performed after the database has been locked and cleaned and this analysis plan has been validated and signed.

5.2 ANALYSIS POPULATIONS

For the purposes of analysis, the following analysis sets are defined.

5.2.1 Full Analysis Population

Modified Intention-to-treat (mITT) analysis set: all randomised participants who received at least one dose of study drug. Participants will be included in the analyses according to the planned randomised intervention.

The following data points sets are defined:

- **DPS1:** All observed data will be included in the analysis set regardless of study intervention discontinuation and/or receipt of rescue therapy
- **DPS2:** For participants who discontinue study intervention and/or receive rescue therapy, post-discontinuation or post-rescue observations will be excluded.

The mITT and DPS1 will be used to estimate the primary endpoints and the all secondary endpoints.

5.2.2 Per Protocol Population

The per-protocol (PP) population will include all participants from the mITT population, with the exception of those who did not meet the inclusion/exclusion criteria or who initially received treatment assigned to the other group.

The PP and DPS2 will be used for sensitivity analyses of the primary endpoint.

5.2.3 Safety Population

Safety analysis set: all participants who are exposed to a study intervention. Participants will be analysed according to the planned randomised intervention.
The safety analysis set is used to analyse the endpoints and assessments related to safety.
Safety analysis set and DPS1 will be used to present safety data.

5.3 HANDLING OF MISSING DATA

The primary and all secondary end points will be analysed on a mITT basis.
During the study, participants may be lost to follow-up, withdraw or drop out. A participant will be considered lost to follow-up if he/she is unreachable for at least two consecutive visits by the study site until the end of the study. And so, for these participants, observations will be censored from the date of last observation.
In addition, for participants still being followed in the study but whose observation is missing at week 48 and at the 30-day visit after week 48, data will be censored at the last observation.
Partial dates will be extrapolated. For example, all dates saved as NK/FEB/2020 will be recoded as 15/FEB/2020 and those saved NK/NK/2020 will be recoded as 30/JUNE/2020. NK means not known.
For the assessment of HIV RNA viral load reduction at week 12, we will use the last observation carried forward approach to fill in missing data at visit 12.
For all continuous variables used as endpoint, if the value is missing at week 48 and the value at the 30-day visit after week 48 is not missing, it will be used to replace the missing week 48 value whether or not the patient has been switched off the study drug.
For participants who stop the study prematurely, if the Early Termination Visit (ETV) is performed, the value will be used to complete the nearest missing visit.
For participants for whom the date of onset of the clinical event used as an endpoint is missing, the missing date of onset will be replaced by the event reporting date.
For patients reported outcomes, we will used multiple imputation approach to fill in missing data.

5.4 INTERIM ANALYSIS

No interim analysis for efficacy was planned. However, an independent data monitoring committee (DSMB) consisting of independent scientists not otherwise involved in the trial has been appointed and has reviewed the data regularly during the study for safety and scientific integrity and has made recommendations to the sponsor.
However, in the event of external evidence of trial interventions, the sponsor may seek advice from the DSMB and the DSMB could recommend an interim efficacy analysis based on the observed data collected at that time to help make a recommendation. A two-sided Type-I error rate of 5% will be used because no formal interim analysis for efficacy is planned.

5.5 MULTIPLE TESTING

Because all subgroup analyses are designed to detect possible heterogeneity of the treatment effect across subgroups, and because they are exploratory and supportive, no adjustment for multiplicity is necessary.

6. SUMMARY OF STUDY DATA

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation (SD), 1st quartile, median, 3rd quartile, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical variables.

The number of patients and the flowchart of the study will be presented. The period of enrolment and the total number of patients screened to be included in the study will be presented. The number of ineligible patients and the total number of randomised patients will be presented. The number of patients who never take the study treatment will also be presented by group and those who remained on the study treatment up to week 48 will be presented.

6.1 SUBJECT DISPOSITION

The number of participants and the flowchart of the study will be presented as in the CONSORT flowchart (Figure 2).

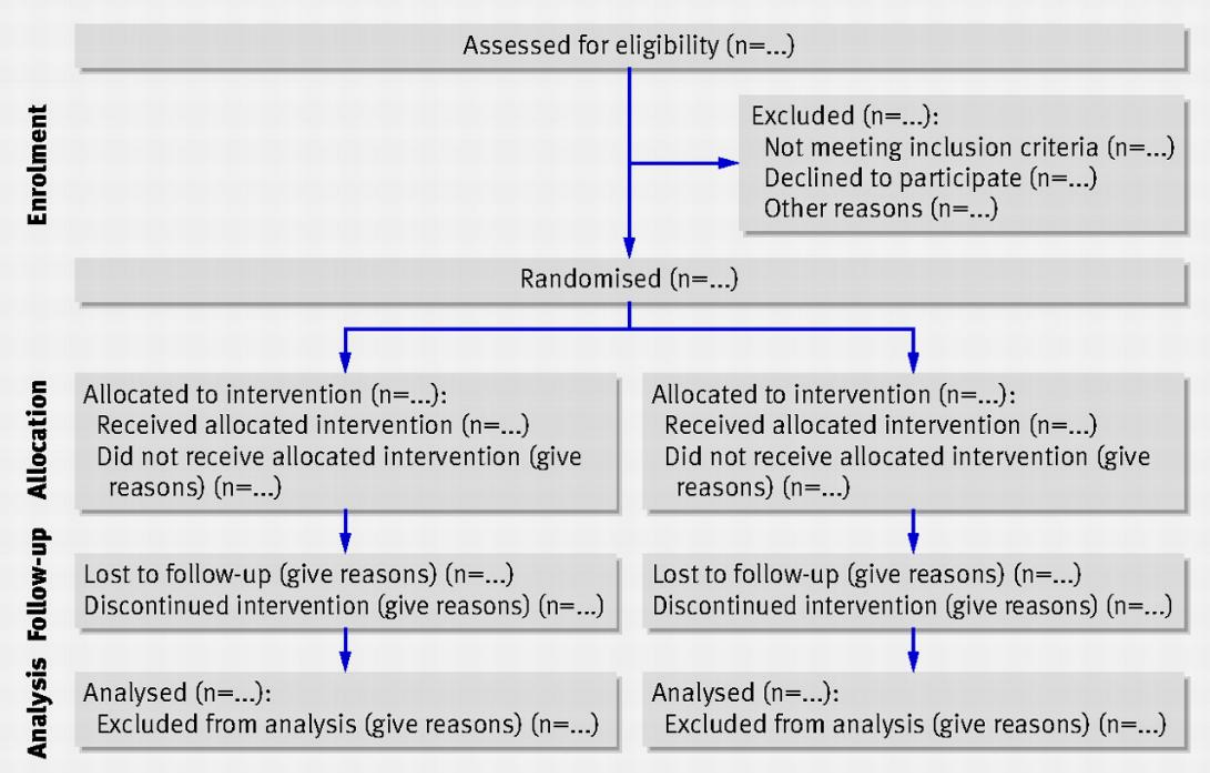

Figure 2: CONSORT flowchart

For the analysis, a summary table with the description of the number of included subjects, the number of randomized subjects, the number of subjects in whom the treatment was initiated, the number of subjects in whom the treatment was not initiated and reasons, the number of subjects who discontinued the study and reasons and when, the number of subjects analyzed, and the number of subjects excluded from the analysis and reasons, will be prepared by treatment group. The dates of the inclusion period will be reported as well as the date of the last follow-up visit. The median (IQR) duration of participation and the total number of person-years will also be reported. The person-year is the total sum of the number of years that each subject of the study population has been under observation. The duration of participation in years for each subject will be calculated by the difference between the date of the last observation and the date of randomization divided by 365.25.

6.2 PROTOCOL DEVIATIONS

The following deviations are defined for the purpose of analysis:

- Did not fulfil the eligibility criteria
- Interruption of study treatment for >10% of total time on treatment
- Received treatment from another randomisation group
- Consent withdrawal
- Lost to follow-up (at least 2 consecutive visits missed until the end of the study)
- At least one missed follow-up visits for those not lost to follow-up

At least one visit for which the viral load is missing for those for whom all visits have been madeA summary table by treatment group and overall with the number and percentage of subjects presenting deviations will be prepared for the subjects in the mITT population.

6.3 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The summary of the demographic and baseline characteristics will be performed on the mITT population. The data will be summarized overall and by randomisation arm (Integrase inhibitor (BIC) versus protease inhibitor (DRV/c)). Baseline data corresponds to all data collected prior to the initiation of the study interventions.

6.3.1 Descriptive statistics

Demographics and baseline characteristics will be summarized as follows:

- For continuous variables: sample size, mean, standard deviation, median, interquartile range, minimum and maximum.
- For categorical variables: sample size, proportion and number of patients in different categories.

6.3.2 Baseline data

The following demographic characteristics will be summarized by treatment group and overall:

- Age
- Sex
- Child bearing potential among Female
- Participating country
- Ethnicity (e.g White caucasian; White mixed; Asian, Black; Other)
- Population group (AIDS with any CD4 cell count; Severe bacterial infection and CD4 cell count < 200; Asymptomatic with CD4 cell count < 100; Currently receiving treatment for an opportunistic infection)
- Body weight and BMI
- Systolic and diastolic Blood Pressure
- Pulse rate
- Alcohol intake (Does not drink alcohol; Drink alcohol)
- Smokers (Never smoked; Current smoker; Ex-smoker)
- Recreational drug use
- Days from HIV diagnosis to treatment initiation
- HIV RNA viral load, log10 copies/mL and in category (<100,000; 100,000-500,000; >500,000)
- CD4+ count (cells/µL) and in category (<50; 50-199; ≥200) and CD4+ (%)
- CD8+ count (cells/µL) and CD8+ (%)
- CD4/CD8 ratio and in category (<0.10; 0.10-0.30; >0.30)
- Positive HBV Antigen; Positive HCV antibody:
- HCV RNA Viral load among those with Positive HCV antibody
- Positive TB testing result
- Red blood cells (10^12/L);
- White blood cells (10^12/L)
- Platelet counts (10^9/L)
- Haemoglobin (g/dL)
- Haematocrit (%)
- MVC (fl)
- MCH (pg)
- Neutrophils (10^{12}/L)
- Lymphocytes (10^{12}/L)
- Monocytes (10^{12}/L)
- Eosinophils (10^{12}/L)
- Basophils (10^{12}/L)Sodium (mmol/L)
- Potassium (mmol/L)
- Total Protein (mmol/L)
- Total Bilirubin (µmol/L)
- Indirect bilirubin (µmol/L)
- ALT (U/L); AST (U/L)Albumin (g/L)
- Creatinine (umol/L); Creatinine clearance (eGFR) (mL/min)
- Alkaline phosphatase (U/L)
- Creatine phosphokinase (U/L)
- Calcium (mmol/L)
- Phosphate (mmol/L)
- Urea (mmol/L)

- Chloride (mmol/L)
- Total cholesterol (mmol/L); HDL-cholesterol (mmol/L); LDL-cholesterol (mmol/L); Triglyceride (mmol/L);
- Glucose (mmol/L)
- Resistance mutations at baseline. Drugs resistance mutations will be identified from the Stanford drugs resistance interpretation algorithm (last version at the time of analysis). https://hivdb.stanford.edu/dr-summary/mut-scores/NRTI/; https://hivdb.stanford.edu/dr-summary/mut-scores/NNRTI/; https://hivdb.stanford.edu/dr-summary/mut-scores/PI/; https://hivdb.stanford.edu/dr-summary/mut-scores/INSTI/.

6.4 STUDY TREATMENT COMPLIANCE

Adherence during the trial will be monitored by subject questioning regarding missed tablets at each visit. Compliance rate for each participant will be estimated by the response of the following item: Thinking about the last week, how often has the subject taken their medication? The response is classified in 5 categories (All the time, Most of the time, About half of the time, Very few times, None). For participants who reported taking their medication “All the time” during the past week, if it is also indicated that they forgot to take their medication at least once since the last visit, they are downgraded to the "Most of the time" category. The compliance rate will be done at each visit. A bar plot will be presented.

6.5 STRATIFICATION FACTOR

The stratification variable is consisted of two variables: participating country (7 countries: UK, Spain, France, Belgium, Germany, Ireland, and Italy) and baseline CD4 cell count (<50, 50-199, ≥200). Overall, 21 strata will be considered. Based on the large number of strata, we anticipated some few participants in some strata. In country that will recruit fewer than 10 participants, we will group together some neighboring countries. In addition, with regard to CD4 cell count, we will group together participants whose value is between 50-199 and ≥200/µl to obtain 2 categories (<50 versus ≥50/µl) because of the anticipated small number of participants in the latter category. These new variables will be used for adjustments.

The number and proportion of participants in each stratum will be reported by treatment group and overall. The exact list of strata will also be presented.

7. EFFICACY ANALYSES

All the efficacy analyses of the primary and secondary endpoints will be conducted on the mITT population and a sensitivity analysis of the per-protocol population.

Time-to-event methods, including Kaplan-Meier, Cox proportional hazard models, and Poisson regression models, will be used to account for all participants in the analysis.

7.1 PRIMARY EFFICACY ANALYSIS

Endpoint

The primary endpoint is the first occurrence of any of the following components:

1. Virological failure
   a) Insufficient virological response, either:
      a. HIV-1 RNA reduction < 1 log 10 copies/mL at week 12, or
      b. Viral load > 50 HIV-1 RNA copies/mL at week 48
   b) Viral rebound, which is subsequently confirmed at the following scheduled or unscheduled visit, defined as either:
      a. Rebound of HIV-1 RNA to >200 copies/mL after having achieved HIV-1 RNA <50 copies/mL
      b. Rebound of HIV RNA by >1 log 10 copies/mL from nadir value, for patients whose viral load has never been suppressed below 50 copies/mL
2. Clinical events[1]
   a) Death related to HIV, AIDS, OI/severe BI or complications of therapy including IRIS
   b) Any new or recurrent AIDS defining event on, or after 28 days of therapy
   c) Any new serious non-AIDS defining event documented by the endpoint review committee (including severe BI, end stage liver disease, renal failure, cardiovascular event, and non-AIDS related malignant disease)
   d) Clinically relevant AEs of any grade or IRIS which require treatment interruption (lasting > 5 days) of INI or boosted PI therapy within the first 48 weeks after randomisation. Discontinuation of BIC or boosted DRV followed by (within 5 days) continuation with another INI or PI, respectively, is not considered as a strategy failure or endpoint.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarized with the number and percentage of participants with an event. Kaplan-Meier curves will also be plotted for the primary endpoint and its component.

A table, listing for each participant any event, they may have had as well as the day from baseline to event onset, will be generated.

Statistical methodology

The proportion of patients with an event will be estimated using the Kaplan-Meier method. Episodes of clinical events diagnosed at baseline will not be considered as incident events in the study. For virological events evaluation data were censored at the time of treatment discontinuation.

The follow-up will begin at baseline and continue until the week 48 visit, study discontinuation, loss to follow-up, or onset of the composite primary endpoint events; whichever occurs first. Participants lost to follow-up or who have discontinued the study when they are endpoint free at time of leaving the study will be censored at the date of last observation.

The effect of study treatment will be assessed using Cox regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell

counts (<50/µL or ≥50/µL), as the sample size would not allow use of the stratification factors of randomisation (country and baseline CD4 in three categories (<50; 50-199; ≥200/µL)). An adjusted hazard ratio (HR) and the associated 95% Confidence Interval (CI) will be calculated. Separate analyses for each component of the primary endpoint will be done. All P-values will be two-tailed with a significant level at 5%.

A sensitive analysis will be performed with the per-protocol population and DPS2.

7.2 SECONDARY EFFICACY ANALYSES

7.2.1 Cumulative incidence of the composite primary endpoint

Endpoint

Cumulative incidence of the composite primary endpoint. All the observed events for each patient over the total duration of follow-up will be considered. Patients with multiple events on a given day will be considered as having one event on that day. For virological events only first episode was considered and data were censored at the time of treatment discontinuation.

Descriptive statistics and graphical representation

The cumulative incidence of the primary composite endpoint will be summarized with the total number of events, person-years, and the incidence rates per 100 person-years by treatment group (Integrase inhibitor versus Protease inhibitor).

Statistical methodology

In this analysis, the event is the sum of all episodes of the composite primary endpoint. For this analysis, the entire follow-up will be considered (i.e. follow-up will begin at baseline and continue until the 48-week visit, study discontinuation, loss to follow-up; whichever occurs first). All participants will be censored on the date of their last observation.

The cumulative incidence of the composite primary endpoint will be estimated by the total number of events divided by the total number of person-years of observation. The person-year is the total sum of the number of years that each subject of the study population has been under observation. The number of years each subject would have been under observation will be calculated by the difference between the date of the last observation and the date of study treatment initiation plus one, divided by 365.25.

The effect of study treatment will be assessed using a Poisson regression model adjusted for the stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL). An adjusted incidence rate ratio (IRR) and the associated 95% CI will be calculated.

All P-values will be two-tailed with a significant level at 5%.

This analysis will only be performed if it is added additional information: i.e. if the number of cumulative episodes is greater than that of the first episode (with at least 10 additional events).

7.2.2 HIV-RNA viral load <50 copies/mL at week 24, 36 and 48

Endpoint

The proportion of patients with HIV-RNA viral load <50 copies/mL at week 24, 36 and 48 using the snapshot approach.

Virologic outcome will be determined by the last available measurement while the participant is on treatment and continues on trial within the time window. The time window for each timepoint is defined in Table A below.

Table A: Proposed Windows		
Visit	**Window (Through End-of-Study Week)**	**Window (Days)**
24	18-30	127-210
36	30-42	211-294
48	42-54	295-378

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarized with the number and percentage of participants with an event.

The proportion of patients with HIV-RNA viral load <50 copies/mL, HIV RNA viral load ≥50 copies/mL, discontinuation due to Adverse Event (AE/SAE), discontinuation due to other reasons or on study but missing data at analysis time point will be calculated. The evolution over time will be analysed graphically using trend analysis.

HIV-RNA ≥ 50 copies/mL includes: patients who changed any component of background therapy to a new drug class, changed background components that were not permitted per protocol, or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48; patients who discontinued study drug or study before Week 48 for lack or loss of efficacy and patients who are equal to or above 50 copies/mL in the 48-week window.

AE/SAE includes: patients who discontinued because of adverse event (AE) or death at any time point from baseline through the time window if this resulted in no virologic data during the specified window.

Other Reasons includes: withdrew consent, loss to follow-up, moved, among others.

Statistical methodology

The proportion of patients with HIV-RNA viral load <50 copies/ml, HIV-RNA viral load ≥50 copies/ml, discontinuation due to adverse event (AE/SAE), discontinuation due to other reasons or participating in the study but with missing data at the time of analysis will be calculated by dividing the number of participants with an event of interest by the total number of participants in the mITT population.

The effect of study treatment on the proportion of patients with HIV-RNA viral load <50 copies/ml at week 24, 36 and 48 will be assessed using a logistic regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). An adjusted odds ratio (OR) and the associated 95% Confidence Interval (CI) will be calculated.

In addition, we will use Cochran-Mantel-Haenszel tests to assess the difference between treatments in the percentage of participants with HIV-RNA viral load <50 copies/ml at week 48 (ie, response rate in BIC group minus the response rate DRV/c group) adjusted for country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µl). All P-values will be two-tailed with a significant level at 5%.

7.2.3 Genotypic resistance test among patients with virological failure

Endpoint

Number and percentage of patients with drugs resistance mutations among patients with virological failure. Drugs resistance mutations will be identified from the Stanford drugs resistance interpretation algorithm (last version at the time of analysis).

https://hivdb.stanford.edu/dr-summary/mut-scores/NRTI/
https://hivdb.stanford.edu/dr-summary/mut-scores/NNRTI/
https://hivdb.stanford.edu/dr-summary/mut-scores/PI/
https://hivdb.stanford.edu/dr-summary/mut-scores/INSTI/.

Descriptive statistics and graphical representation

The analyses will be performed on patients with virological failure in the mITT population for whom genotypic sequences have been obtained. Data will be summarized with the number and percentage of participants with drugs resistance mutations.

Statistical methodology

The proportion of participants with drugs resistance mutations will be calculated by dividing the number of participants with drug resistance mutations by the total number of participants with virological failure for whom genotypic sequences have been obtained. The frequency of each resistance mutation will be indicated.

Fisher's exact test will be used to compare the presence of at least one drug resistance mutation between the 2 groups.

7.2.4 Time to reach CD4 cell count >200/µl

Endpoint

The median time to reach CD4 cell count >200/µl.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population with CD4≤200/µL at baseline and DPS1. Data will be summarized with the number and percentage of participants achieving a CD4 cell count >200/µl and the median (95% CI) time to reach a CD4 cell count >200/µl. Kaplan-Meier curves will also be plotted.

Statistical methodology

Kaplan-Meier method will be used to estimate the proportion of participants achieving a CD4 cell count >200/µl and the median time to achieve a CD4 cell count >200/µl. The follow-up will begin at baseline (date of study treatment initiation) and continue until the week 48 visit, study discontinuation, loss to follow-up, or onset of a CD4 cell count >200/µl; whichever occurs first. Participants lost to follow-up or who have discontinued the study with a CD4≤ 200/µl will be censored at the date of last observation.

The effect of study treatment on the time to reach a CD4 >200/µl will be assessed using Cox regression model with adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). An adjusted HR and the associated 95% CI will be calculated. All P-values will be two-tailed with a significant level at 5%.

7.2.5 CD4 cell count <200/µl and <350 at week 4, 8, 12, 24, 36 and 48

Endpoints

- The proportion of patients with CD4 cell count <200/µl at week 4, 8, 12, 24, 36 and 48
- The proportion of patients with CD4 cell count <350/µl at week 4, 8, 12, 24, 36 and 48

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarized with the number and percentage of participants CD4 cell count <200/µl and <350/µl. The evolution over time will be analysed graphically using trend analysis.

Statistical methodology

The evolution of the proportion of participants with CD4<200/µl and <350/µl over time will be compared between the 2 treatment groups (DRV/c versus BIC) using a Generalized Estimating Equation (GEE) models with independent covariance structure, binomial distribution and log link, to estimate the relative risk. The models will include treatment group, time, and interaction between treatment group and time. Time will be modelled as categorical variable. A relative risk (RR) and the associated 95% CI will be calculated. All P-values will be two-tailed with a significant level at 5%.

7.2.6 Change in CD4/CD8 ratio from baseline to week 48

Endpoints

The change in CD4/CD8 ratio from baseline to week 48.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarized in tables by mean and standard error. The evolution of CD4/CD8 ratio will be described by boxplots for each treatment group at each time point. The number of participants with data available at each time point will also be reported.

Statistical methodology

The mean change in CD4/CD8 ratio from baseline to week 48 will be compared between the 2 treatment groups using a mixed model with random intercept and slope and spatial power covariance structure due to unequal time intervals between visits. The models included treatment group, time, and interaction between treatment group and time. Time was modelled as a categorical variable. All P-values will be two-tailed with a significant level at 5%.

7.2.7 Incidence of IRIS

Endpoints

The endpoint is the first occurrence of IRIS over the 48-week visit. IRIS diagnosed at baseline will not be considered in the analysis.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarized with the number and percentage of participants with an IRIS. Kaplan-Meier curves will also be plotted.

Statistical methodology

The incidence of IRIS will be estimated with the Kaplan-Meier method. The follow-up will begin at baseline (date of study treatment initiation) and continue until the week 48 visit, study discontinuation or death, loss to follow-up, or onset of IRIS; whichever occurs first.

The effect of study treatment will be assessed using Cox regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). An adjusted hazard ratio (HR) and the associated 95% Confidence Interval (CI) will be calculated.

7.2.8 Incidence of hospitalisation

Endpoints

The endpoint is the first occurrence of hospitalisation over the 48-week visit. Hospitalisation occurring before the initiation of study treatment (baseline) will not be considered in the analysis.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarized with the number and percentage of hospitalised participants. The Kaplan-Meier curves will also be plotted.

Statistical methodology

The incidence of hospitalisation will be estimated with the Kaplan-Meier method. The follow-up will begin at baseline (date of study treatment initiation) and continue until the week 48 visit, study discontinuation or death, loss to follow-up, or hospitalisation; whichever occurs first.

The effect of study treatment will be assessed using Cox regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). An adjusted hazard ratio (HR) and the associated 95% Confidence Interval (CI) will be calculated.

7.2.9 Duration of hospitalisation

Endpoints

The endpoint is the duration of the hospitalisation during the 48-week period. The event of interest is the occurrence of last discharge (end date of hospitalisation) from hospital. A transfer to a palliative care will not be considered a discharge. Hospitalisation occurring before the initiation of study treatment (baseline) will not be considered in the analysis.

Descriptive statistics and graphical representation

The analyses will be performed with the hospitalised patients in the mITT population and DPS1. Data will be summarized with the number and percentage of participants discharged from hospital, and the median (95% CI) duration of hospitalisation. The Kaplan-Meier curves will also be plotted.

Statistical methodology

The proportion of participants discharged from hospital and the median duration of hospitalisation will be estimated using the Kaplan-Meier method. Follow-up will begin at the date of first hospitalisation and continue until the week 48 visit, study discontinuation or death, loss to follow-up, or last discharge from hospital; whichever occurs first.

The effect of study treatment will be assessed using Cox regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). An adjusted hazard ratio (HR) and the associated 95% Confidence Interval (CI) will be calculated.

7.2.10 Rate of relapse recurrence of specific opportunistic infection or bacterial infection through week 48

Endpoint

The endpoint is the rate of relapse/recurrence of specific opportunistic infection or bacterial infection through week 48.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarized with the number and percentage of participants with relapse/recurrence of specific opportunistic infection or bacterial infection through week 48.

Statistical methodology

The rate of relapse/recurrence will be estimated by the number of patients with relapse/recurrence divided by the total number patients in ITT population.

The effect of study treatment on the rate of relapse/recurrence of specific opportunistic infection or bacterial infection at week 48 will be assessed using a logistic regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). An adjusted odds ratio (OR) and the associated 95% Confidence Interval (CI) will be calculated.

8. SAFETY ANALYSES

Endpoints

Safety endpoints include the following endpoints:

- Cumulative incidence of any adverse events (AEs: grade ≥2), separately grade 2, 3 and 4 AE
- Cumulative incidence grade 3 or AEs
- Cumulative incidence of drug-related AEs (all grade)
- Cumulative incidence of drug-related grade 3 and 4 AEs
- Cumulative incidence of serious adverse events (SAE)
- Cumulative incidence of AE leading to study/treatment
- Cumulative incidence of laboratory toxicities
- Death

Participants with multiple adverse events on a given day will be considered as having one adverse event on that day. Adverse events occurring before the initiation of study treatment (baseline) will not be considered in the analysis.

Descriptive statistics and graphical representation

All analyses on safety endpoints will be performed on the Safety analysis set. All observed data will be included in the analysis set.

Any AE (grade ≥2), grade 3 or 4 AE, SAE, drug-related SAE, grade 2, 3 and 4 AEs, drug-related grade 3/4 AE, drug-related AEs (all grade), discontinuation of study/treatment due AEs, laboratory toxicities and death will be summarized with the total number of events, number and percentage of participants with at least one event and the incidence rates per 100 person-years of these events by treatment group (BIC versus DRV/c). The most frequent drug-related grade 3 or 4 AEs will be reported.

Statistical methodology

The incidence rates of each endpoint of interest will be calculated by the total number of events from baseline to week 48 visit divided by the total number of person-years. In this analysis, the entire

follow-up will be considered (i.e. follow-up will begin at baseline and continue until the week 48 visit, study discontinuation or death, loss to follow-up; whichever occurs first). The duration in years of participation for each subject will be calculated by the difference between the date of the last observation and the date of date of study treatment initiation plus one, divided by 365.25. The person-years is the total sum of the number of years that each member of a study population has been under observation.

The incidence rates of each endpoint will be compared between the treatment groups (BIC versus DRV/c) with a Poisson regression model adjusted for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). The incidence rates ratio and the associated 95% confidence interval will be calculated. All P-values will be two-tailed with a significant level at 5%.

9. SUBGROUP ANALYSES

Subgroup analyses for the composite primary endpoints will be performed to assess the consistency of the effect of study treatment across the subgroups. The analysis will be performed with the mITT population. The following baseline variables will be studied (continuous variables will be categorized into terciles):

- age at inclusion (categorized into terciles)
- country
- group of neighbouring countries
- baseline CD4 cell counts (<50 or 50-199 or ≥200/µL)
- baseline CD4 cell counts (<50 or ≥50/µL)
- gender
- transmission group
- ethnic group
- baseline viral load (<100,000, 100,000-500,000, >500,000)
- Current smoker (no or yes)
- adherence (take medication all the time versus not at all)

If the number of participants is too small (less than 10) within a subgroup, then the subgroup categories may be redefined before locking the database. A forest plot will display confidence intervals across subgroups.

We will use a Cox proportional hazard model to calculate the hazard ratio between BIC and DRV/c of the incidence of the first episode of the composite primary endpoint event in each subpopulation, without adjustments for stratification factors. The heterogeneity of the effect of BIC and DRV/c within subgroups will be assessed by including terms for interactions between treatment group and subgroup variables in a Cox proportional hazard model.

10. OTHER ANALYSES

10.1 OTHER SECONDARY ENDPOINTS

10.1.1 ART and/or opportunistic infection/bacterial infection treatment changes and/or dose modifications due to toxicities and/or DDI with ART, and/or IRIS through week 48

Endpoint

The endpoint is the proportion of patients with ART treatment changes and/or dose modifications due to toxicities and/or DDI with ART, and/or IRIS through week 48.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarised with the number and percentage of participants with ART or OI/BI treatment changes or dose modifications due to toxicities and DDI and IRIS through week 48. The list of patients with the event of interest will be reported in a table, including the previous and the current treatment, start date, end date and the reason for change.

Statistical methodology

The percentage of patients with ART n treatment changes due to toxicities and/or DDI with ART, and/or IRIS will be estimated by the number of patients with the event of interest divided by the total number patients in ITT population. The effect of study treatment on the proportion of patients with ART treatment changes due to toxicities and/or DDI with ART, and/or IRIS at week 48 will be assessed using a logistic regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/μL)). An adjusted odds ratio (OR) and the associated 95% Confidence Interval (CI) will be calculated. Similar analyses will also be performed separately for each component (toxicities, DDI, and IRIS). If no events were observed in a group, the comparison will be made using Fisher's exact test.

10.1.2 Health care resource use, through week 48

Endpoint

The endpoint is the proportion of patients with health care resource use, through week 48.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarised with the number and percentage of participants with health care resource use, including total inpatient days and emergency room visits through week 48.

Statistical methodology

The percentage of patients with health care resource use, including total inpatient days and emergency room visits will be estimated by the number of patients with the event of interest divided by the total number patients in ITT population.

The effect of study treatment on the proportion of patients with health care resource use, including total inpatient days and emergency room visits at week 48 will be assessed using a logistic regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). An adjusted odds ratio (OR) and the associated 95% Confidence Interval (CI) will be calculated.

10.1.3 Quality of life (EQ-5D-3L questionnaire) and HIV Symptoms index

Endpoints

The endpoints are:

- Change from baseline in health status score ranging from 0 to 100 (100 being best quality of life) and in each of the 5 dimensions of the EQ-5D-3L quality of life questionnaires (mobility, self- care, usual activities, pain/discomfort and anxiety/depression). Each dimension has 3 levels: 1=no problems, 2=some problems, and 3=extreme problems.
- Change from baseline in HIV symptoms index score over time. HIV Symptoms Index questionnaire is consisted of 20 selected symptoms. Each symptom has 5 levels: 0=I do not have this symptom 1=It doesn't bother me 2=It bothers me a little 3=It bothers me 4=It bothers me a lot. The HIV Symptom Index score is the sum of frequency ratings for the 20 selected symptoms; the score could range from 0 to 80.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population who complete the baseline questionnaire and least one of the follow-up questionnaires.

Data for health status score and HIV Symptoms index will be summarised by mean and standard error. The evolution of health status score and HIV Symptoms index will be described by boxplots for each treatment group at each time point.

Data for the 5 dimensions will be summarised with number and percentages per class and Bar plotted will also be generated for each of the 5 dimensions.

The number of participants with data available at each time point will also be reported.

Statistical methodology

The changes from baseline in health status score will be compared between the two treatment groups using mixed models for repeated measures with random intercept and slope and spatial power covariance structure due to unequal time intervals between visits, adjusted for country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL). The model will include treatment group, time, interaction between treatment group and time, country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL). Time will be modelled as categorical variables.

The distribution of each of the 5 dimensions (mobility, self- care, usual activities, pain/discomfort and anxiety/depression), will be compared between the two treatment groups at each timepoint using Chisquare test

The changes from baseline in Symptom index score will be compared between the two treatment groups using mixed models for repeated measures with random intercept and slope and spatial power covariance structure due to unequal time intervals between visits, adjusted for country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL). The model will include treatment group, time, interaction between treatment group and time, country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL). Time will be modelled as categorical variables. All p-values will be two-tailed, with a significant level of 0.05.

10.1.4 discontinuation or modification of study medication due to insufficient virological response or resistance mutation development before week 48

Endpoints

The endpoint is the proportion of patients with discontinuation or modification of study medication due to insufficient virological response or resistance mutation development before week 48.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarised with the number and percentage of participants with discontinuation or modification of study medication due to insufficient virological response or resistance mutation development through week 48. The list of patients with the event of interest will be reported in a table, including the reasons for discontinuation or modification of study medication.

Statistical methodology

The percentage of patients with discontinuation or modification of study medication due to insufficient virological response or resistance mutation development will be estimated by the number of patients with the event of interest divided by the total number patients in ITT population.

The effect of study treatment on the proportion of patients with discontinuation or modification of study medication due to insufficient virological response or resistance mutation development through week 48 will be assessed using a logistic regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). An adjusted odds ratio (OR) and the associated 95% Confidence Interval (CI) will be calculated.

The analyses will also be performed separately for each component of the endpoint (insufficient virological response and resistance mutation development). If no events were observed in a group, the comparison will be made using Fisher's exact test.

10.1.5 Adherence to study medication over time

Endpoints

Adherence during the trial will be monitored by subject questioning regarding missed tablets at each visit. Compliance rate for each participant will be estimated by the response of the following item: Thinking about the last week, how often has the subject taken their medication? The response is classified in 5 categories (All the time, Most of the time, About half of the time, Very few times, None).

Descriptive statistics and graphical representation

Analyses will be performed with the mITT population for which data are available at each time point. The data will be summarized by the number and percentage of participants per class at each time point. A bar chart will be presented.

Statistical methodology

The analysis will be descriptive and no inference will be made.

10.1.6 Change from baseline in plasma and urine laboratory parameters

Endpoints

The endpoints are the change from baseline plasma and urine laboratory parameters

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DSP1.

Data will be summarised by mean and standard error. The evolution will be described by boxplots for each treatment group at each time point.

Statistical methodology

The changes from baseline in haematology, chemistry, lipid and glycaemia will be compared between the two treatment groups using mixed models for repeated measures with random intercept and slope and spatial power covariance structure due to unequal time intervals between visits, adjusted for country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL). The model will include treatment group, time, interaction between treatment group and time, country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL). Time will be modelled as categorical variables.

All p-values will be two-tailed, with a significant level of 0.05.

10.2 EXPLANATORY ENDPOINTS

10.2.1 Mutations detected by deep sequencing compared with those detected by population sequencing

Endpoint

The endpoint is the proportion of patients for whom there is a difference in the list of mutations (Stanford list last available version) detected by deep sequencing compared with those detected by population sequencing.

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarized with the number and percentage of participants with difference in the list of mutations detected by deep sequencing compared with those detected by population sequencing.

Statistical methodology

The proportion of patients with difference in the list of mutations detected by deep sequencing compared with those detected by population sequencing will be estimated by dividing the number of participants with difference in the list of mutations detected by deep sequencing compared with those detected by population sequencing by the total number of participants in the mITT population.

The effect of study treatment on the proportion patients with difference in the list of mutations detected by deep sequencing compared with those detected by population sequencing will be assessed using a logistic regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). An adjusted odds ratio (OR) and the associated 95% Confidence Interval (CI) will be calculated.

10.2.2 Proportion of patients with HIV RNA viral load <50 copies/mL at week 4, 8, and 12

Endpoint

The endpoint is the proportion of patients with HIV-RNA viral load <50 copies/mL at week 4, 8 and 12 using the snapshot approach.

Virologic outcome will be determined by the last available measurement while the participant is on treatment and continues on trial within the time window. The time window for each timepoint is defined in Table B below.

Table B: Proposed Windows

Visit	Window (Through End-of-Study Week)	Window (Days)
4	2-6	15-42
8	6-10	43-70
12	10-14	71-98

Descriptive statistics and graphical representation

The analyses will be performed with the mITT population and DPS1. Data will be summarized with the number and percentage of participants with an event.

Statistical methodology

The proportion of patients with HIV-RNA viral load <50 copies/mL will be estimated by dividing the number of participants with HIV-RNA viral load <50 copies/mL by the total number of participants in the mITT population.

The effect of study treatment on the proportion patients with HIV-RNA viral load <50 copies/ml at week 4, 8, and 12 will be assessed using a logistic regression model with treatment group and adjustments for stratification factor (country/group of neighbouring countries and baseline CD4 cell counts (<50 or ≥50/µL)). An adjusted odds ratio (OR) and the associated 95% Confidence Interval (CI) will be calculated.

10.2.3 Evolution of HIV RNA in individuals with viral load >50 copies/mL at week 48

Endpoint

The endpoint is the evolution of HIV RNA between week 48 and week 52 in individuals with viral load >50 copies/mL at week 48.

Descriptive statistics and graphical representation

Analyses will be performed in participants with HIV RNA viral load >50 copies/mL at week 48. Data will be summarized for each treatment group: (i) the number of participants with 50-200 HIV RNA at week 48 and a viral load increasing by >200 copies/mL, remaining at 50-200 copies/mL or decreasing to <50 copies/mL at week 52. (ii) the number of participants with >200 HIV RNA at week 48 and a viral load remaining at >200 copies/mL, decreasing to 50-200 copies/mL or decreasing to <50 copies/mL at week 52. The evolution between week 48 and 52 will be analysed graphically using trend analysis.

Statistical methodology

A descriptive analysis will be carried out and no statistical inferences will be made.

1. REPORTING CONVENTIONS

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.

Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

2. STATISTICAL SOFTWARE

Statistical analyses will be performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA). Stata version 15.0 (StataCorp, College Station, TX, USA) will be used for graphical representation of selected analyses.

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4. LISTING OF TABLES AND FIGURES

TABLE 1. BASELINE CHARACTERISTICS

	Integrase inhibitor (N=XXX)	Protease inhibitor (N=XXX)	Total (N=XXX)
Age (years), median (IQR)			
Gender			
Male			
Female			
Child bearing potential			
Ethnicity			
White caucasian			
White mixed			
Asian			
Black			
African			
Caribbean			
Other			
Prior AIDS-defining event			
No			
Yes			
Days from HIV diagnosis to treatment initiation, median (IQR)			
HIV RNA viral load, log10 copies/mL, median (IQR)			
<100,000			
100,000 – 500,000			
>500,000			
CD4+ count (cells/µL)			
<50			
50 – 199			
≥200			
CD4+ (%)			
CD8+ count (cells/µL), median (IQR)			
CD8+ (%)			
CD4/CD8 ratio, median (IQR)			
<0.10			
0.10 – 0.30			
>0.30			
Alcohol intake			
Does not drink alcohol			
Drinks alcohol			
Current Smokers			
Never smoked			
Current smoker			
Ex smoker			
Recreational drug use			
Positive HBV Antigen			
Positive HCV antibody			
HCV RNA VL, median (IQR)			
Positive TB testing result			
Body mass index (BMI, kg/m2)			
Weight, Kg			
Systolic Blood Pressure (mmHg)			
Diastolic Blood Pressure (mmHg)			
Pulse rate			
Red blood cells (10^12/L)			
White blood cells (10^12/L)			
Platelet counts (10^9/L)			
Haemoglobin (g/dL)			

Hematocrit (%)
MVC (fl)
MCH (pg)
Neutrophils (10^{12}/L)
Lymphocytes (10^{12}/L)
Monocytes (10^{12}/L)
Eosinophils (10^{12}/L)
Basophils (10^{12}/L)
Potassium (mmol/L)
Total Protein (mmol/L)
Sodium (mmol/L)
ALT (U/L)
Total Bilirubin (umol/L)
Indirect bilirubin (umol/L)
ALT (U/L) ; AST (U/L)
Albumin (g/L)
Creatinine (umol/L)
Creatinine clearance (eGFR) (mL/min)
Alkaline phosphatase (U/L)
Creatinine phosphokinase (U/L)
Calcium (mmol/L)
Urea (mmol/L)
Phosphate (mmol/L)
Chloride (mmol/L)
Fasting plasma lipids and glucose
Total cholesterol (mmol/L)
HDL-cholesterol (mmol/L)
LDL-cholesterol (mmol/L)
Triglyceride (mmol/L)
Glucose (mmol/L)

TABLE 1B: BASELINE RESISTANCE MUTATIONS

Characteristic		Integrase inhibitor (N=XXX)	Protease inhibitor (N=XXX)	Total (N=XXX)
Resistance testing, n (%)				
	No			
	Yes			
Resistance mutations to ARV class				
	NRTI			
	NNRTI			
	PI			
	INI			
NRTI mutations (Stanford algorthm last version)				
NNRTI mutations (Stanford algorthm last version)				
PI mutations (Stanford algorthm last version)				
INI mutations (Stanford algorthm last version)				
Resistance to DRV (stanford algorithm)				
	Resistance			
	Intermediate			
	Sensitive			
Resistance to BIC (stanford algorithm)				
	Resistance			
	Intermediate			
	Sensitive			
Resistance to 3TC/FTC (stanford algorithm)				
	Resistance			
	Intermediate			
	Sensitive			
Resistance to TAF (stanford algorithm)				
	Resistance			
	Intermediate			
	Sensitive			
Resistance to TDF (stanford algorithm)				
	Resistance			
	Intermediate			
	Sensitive			

TABLE 2. PRIMARY COMPOSITE ENDPOINT AND ITS COMPONENT

	mITT analysis			PP analysis		
	Integrase Inhibitor	**Protease Inhibitor**	**Adjusted Hazard ratio**	**Integrase Inhibitor**	**Protease Inhibitor**	**Adjusted Hazard ratio**
	N=XXX	**N=XXX**		**N=XXX**	**N=XXX**	
Primary composite endpoint						
Virological failure						
Insufficient virological response						
Viral rebound						
Clinical events						
Any new or recurrent AIDS defining event on, or after 28 days of therapy						
SAE due to Non-AIDS events						
AE leading to discontinuation						
Death						

Insufficient virologic response: (HIV-1 RNA reduction < 1 log 10 copies/mL at week 12, or Viral load > 50 HIV-1 RNA copies/mL at week 48).

Viral rebound: confirmed rebound of HIV-1 RNA to >200 copies/mL after having achieved HIV-1 RNA <50 copies/mL, or confirmed rebound of HIV RNA by >1 log 10 copies/mL from nadir value, for patients whose viral load has never been suppressed below 50 copies/mL.

TABLE 2B. CUMULATIVE INCIDENCE OF THE PRIMARY COMPOSITE ENDPOINT

	Integrase Inhibitor (N=xxx)			**Protease Inhibitor (N=xxx)**			**Adjusted Incidence rate ratio (95% CI)**	**p-value**
	N of event	*Person-years*	*IR per 100 p-y*	*N of event*	*Person-years*	*IR per 100 p-y)*		
Composite Primary endpoint								

All observed endpoint will be considered in the analysis. In this analysis, the entire follow-up will be considered (i.e. follow-up began at baseline and continued until the end of the study, study discontinuation, loss to follow-up; whichever occurs first). The incidence rates will be calculated by the total number of events from baseline to the end of the study divided by the total number of person-years. The incidence rates will be compared between the treatment groups (Integrase inhibitor versus Protease inhibitor) with a Poisson regression model adjusted for stratification factor. The incidence rates ratio and the associated 95% confidence interval will be calculated.

TABLE 3. HIV-RNA VIRAL LOAD <50 COPIES/ML AT WEEK 24, 36 AND 48

		Integrase Inhibitor		Protease Inhibitor		Adjuted OR	adjusted difference
		N=XXX		N=XXX		(95% CI)	(95% CI)
		N	% (95% CI)	N	% (95% CI)		
	HIV-RNA < 50 copies/mL						
	HIV-RNA ≥ 50 copies/mL						
	Data in window not below 50 copies/mL						
	Discontinued for lack of efficacy						
W24	Change in backgroud therapy						
	No virologic data						
	Discontinuation due to AE/SAE						
	Discontinuation due for other reason						
	On study but missing data in window						
	HIV-RNA < 50 copies/mL						
	HIV-RNA ≥ 50 copies/mL						
	Data in window not below 50 copies/mL						
	Discontinued for lack of efficacy						
W36	Change in backgroud therapy						
	No virologic data						
	Discontinuation due to AE/SAE						
	Discontinuation due for other reason						
	On study but missing data in window						
	HIV-RNA < 50 copies/mL						
	HIV-RNA ≥ 50 copies/mL						
	Data in window not below 50 copies/mL						
	Discontinued for lack of efficacy						
W48	Change in backgroud therapy						
	No virologic data						
	Discontinuation due to AE/SAE						
	Discontinuation due for other reason						
	On study but missing data in window						

TABLE 4. OTHER SECONDARY EFFICACY ENDPOINTS

	Integrase Inhibitor	Protease Inhibitor	Adjusted Hazard ratio	P-value
	N=XXX	N=XXX		
Kaplan-Meier estimate of percentage of patients with CD4>200/µL, n (%)				
Kaplan-Meier estimate of median (95% CI) time to reach CD4>200/µL				
Kaplan Meier estimate of incidence of IRIS, n (%)				
Kaplan-Meier estimate of Incidence of hospitalisations, , n (%)				
Kaplan-Meier estimate of median (95% CI) duration of hospitalisation				

TABLE 5: EVOLUTION OF CD4 CELL COUNT <200/µL AND <350 AT WEEK 4, 8, 12, 24, 36 AND 48

	CD4 cell count <200/µL			CD4 cell count <350/µL		
Week	Integrase Inhibitor	Protease Inhibitor	P-value between groups	Integrase Inhibitor	Protease Inhibitor	P-value between groups
	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
0						
4						
8						
12						
24						
36						
48						
RR (95% CI) from baseline to W4						
RR (95% CI) from baseline to W8						
RR (95% CI) from baseline to W12						
RR (95% CI) from baseline to W24						
RR (95% CI) from baseline to W36						
RR (95% CI) from baseline to W48						

TABLE 6: EVOLUTION OF CD4/CD8 RATIO AT WEEK 4, 8, 12, 24, 36 AND 48

	CD4/CD8 ratio		
Week	Integrase Inhibitor	Protease Inhibitor	P-value between groups
	Mean (SD)	Mean (SD)	
0			
4			
8			
12			
24			
36			
48			
Mean (95% CI) difference from baseline to week 4			
Mean (95% CI) difference from baseline to week 8			
Mean (95% CI) difference from baseline to week 12			
Mean (95% CI) difference from baseline to week 24			
Mean (95% CI) difference from baseline to week 36			
Mean (95% CI) difference from baseline to week 48			

TABLE 7: SAFETY

	Integrase inhibitor (N=XXX) Person-Year (P-Y): XXX.X			Protease inhibitor (N=XXX) Person-Year (P-Y): XXX.X			P-value
	N of events	N of pts (%)	Incidence rate/100 p-y	N of events	N of pts (%)	Incidence rate/100 p-y	
Any adverse events (AEs : grade ≥2)							
Grade 2							
Grade 3							
Grade 4							
Grade unknown							
Grade 3 or 4 AE							
Drug related AEs							
Drug related grade ¾ AEs							
dress syndrom (rash)							
IRIS							
IRIS-Kaposis sarcoma							
PML-IRIS requiring hospitalisation							
progressive rash							
transaminitis							
worsening symptoms of Progressive multifocal leukoencephalopathy							
….							
….							
AE leading to the study drugs interruption							
Serious adverse events (SAE)							
Laboratory toxicities							
Death							

TABLE 8. OTHER SECONDARY ENDPOINTS

	Integrase Inhibitor	Protease Inhibitor	Adjusted OR	P-value
	N=XXX	N=XXX	(95% CI)	
Percentage of patients with HIV drug resistance mutations among those with virological failure				
Proportion of patients with ART treatment changes due to toxicities and/or DDI with ART, and/or IRIS through week 48 - due to toxicities - due to DDI - due to IRIS				
Proportion of patients with with health care resource use, including total inpatient days and emergency room visits through week 48				
Proportion of patients with discontinuation or modification of study medication due to insufficient virological response or resistance mutations development before week 48 - for insufficient virological response - resistance mutations development				
Proportion of patients for whom there is a difference in the list of mutations (Stanford list last available version) detected by deep sequencing compared with those detected by population sequencing				

TABLE 9: EVOLUTION OF QUALITY OF LIFE (HEALTH STATUS SCORE) AND HIV SYMPTOMS INDEX

	QOL : health status score			HIV Symptoms index score		
Week	**Integrase Inhibitor**	**Protease Inhibitor**	**P-value between groups**	**Integrase Inhibitor**	**Protease Inhibitor**	**P-value between groups**
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
0						
4						
8						
12						
24						
36						
48						
Mean (SD) from baseline to W4						
Mean (SD) from baseline to W8						
Mean (SD) from baseline to W12						
Mean (SD) from baseline to W24						
Mean (SD) from baseline to W36						
Mean (SD) from baseline to W48						

TABLE 10: QUALITY OF LIFE DIMENSIONS: MOBILITY AND SELF- CARE

	Mobility			Self- care		
Week	**Integrase Inhibitor**	**Protease Inhibitor**	**P-value between groups**	**Integrase Inhibitor**	**Protease Inhibitor**	**P-value between groups**
	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
0 1=no problems, 2=some problems, 3=extreme problems						
4 1=no problems, 2=some problems, 3=extreme problems						
8 1=no problems, 2=some problems, 3=extreme problems						
12 1=no problems, 2=some problems, 3=extreme problems						
24 1=no problems, 2=some problems, 3=extreme problems						
36 1=no problems, 2=some problems, 3=extreme problems						
48 1=no problems, 2=some problems, 3=extreme problems						
RR (95% CI) from baseline to W4						
RR (95% CI) from baseline to W8						
RR (95% CI) from baseline to W12						
RR (95% CI) from baseline to W24						
RR (95% CI) from baseline to W36						
RR (95% CI) from baseline to W48						

TABLE 11: QUALITY OF LIFE DIMENSIONS: USUAL ACTIVITIES AND PAIN/DISCOMFORT

	Usual activities			Pain/discomfort		
Week	**Integrase Inhibitor**	**Protease Inhibitor**	**P-value between groups**	**Integrase Inhibitor**	**Protease Inhibitor**	**P-value between groups**
	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
0 1=no problems, 2=some problems, 3=extreme problems						
4 1=no problems, 2=some problems, 3=extreme problems						
8 1=no problems, 2=some problems, 3=extreme problems						
12 1=no problems, 2=some problems, 3=extreme problems						
24 1=no problems, 2=some problems, 3=extreme problems						
36 1=no problems, 2=some problems, 3=extreme problems						
48 1=no problems, 2=some problems, 3=extreme problems						
RR (95% CI) from baseline to W4						
RR (95% CI) from baseline to W8						
RR (95% CI) from baseline to W12						
RR (95% CI) from baseline to W24						
RR (95% CI) from baseline to W36						
RR (95% CI) from baseline to W48						

TABLE 12: QUALITY OF LIFE DIMENSIONS: ANXIETY/DEPRESSION

	Anxiety/depression		
Week	**Integrase Inhibitor**	**Protease Inhibitor**	**P-value between groups**
	n/N (%)	n/N (%)	
0 1=no problems, 2=some problems, 3=extreme problems			
4 1=no problems, 2=some problems, 3=extreme problems			
8 1=no problems, 2=some problems, 3=extreme problems			
12 1=no problems, 2=some problems, 3=extreme problems			
24 1=no problems, 2=some problems, 3=extreme problems			
36 1=no problems, 2=some problems, 3=extreme problems			
48 1=no problems, 2=some problems, 3=extreme problems			
RR (95% CI) from baseline to W4			
RR (95% CI) from baseline to W8			
RR (95% CI) from baseline to W12			
RR (95% CI) from baseline to W24			
RR (95% CI) from baseline to W36			
RR (95% CI) from baseline to W48			

TABLE 13. HIV-RNA VIRAL LOAD <50 COPIES/ML AT WEEK 4, 8 AND 12

		Integrase Inhibitor		Protease Inhibitor		Adjuted OR	adjusted difference
		N=XXX		N=XXX		(95% CI)	(95% CI)
		N	% (95% CI)	N	% (95% CI)		
	HIV-RNA < 50 copies/mL						
	HIV-RNA ≥ 50 copies/mL						
	Data in window not below 50 copies/mL						
	Discontinued for lack of efficacy						
W4	Change in backgroud therapy						
	No virologic data						
	Discontinuation due to AE/SAE						
	Discontinuation due for other reason						
	On study but missing data in window						
	HIV-RNA < 50 copies/mL						
	HIV-RNA ≥ 50 copies/mL						
	Data in window not below 50 copies/mL						
	Discontinued for lack of efficacy						
W8	Change in backgroud therapy						
	No virologic data						
	Discontinuation due to AE/SAE						
	Discontinuation due for other reason						
	On study but missing data in window						
	HIV-RNA < 50 copies/mL						
	HIV-RNA ≥ 50 copies/mL						
	Data in window not below 50 copies/mL						
	Discontinued for lack of efficacy						
W12	Change in backgroud therapy						
	No virologic data						
	Discontinuation due to AE/SAE						
	Discontinuation due for other reason						
	On study but missing data in window						

TABLE 14: ADHERENCE TO STUDY MEDICATION OVER TIME

			Randomisation			
			Integrase inhibitor N=xxx		Protease inhibitor N=xxx	
			N	%	N	%
WK12	How often has patient taken medication?	All the time				
		Most of the time				
		About half the time				
		Very few times				
		None				
	Total					
WK24	How often has patient taken medication?	All the time				
		Most of the time				
		About half the time				
		Very few times				
		None				
	Total					
WK36	How often has patient taken medication?	All the time				
		Most of the time				
		About half the time				
		Very few times				
		None				
	Total					
WK48	How often has patient taken medication?	All the time				
		Most of the time				
		About half the time				
		Very few times				
		None				
	Total					

TABLE 15: CHANGE FROM BASELINE IN LABORATORY RESULTS

Laboratory parameters	Week	**Integrase Inhibitor N=xxx**		**Protease Inhibitor N=xxx**		**P-value between groups**
		N	Mean (SE)	N	Mean (SE)	
Red blood cells (10^12/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
White blood cells (10^12/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Platelet counts (10^9/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Haemoglobin (g/dL)	0					
	4					

	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Hematocrit (%)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
MVC (fl)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
MCH (pg)	0					
	4					
	8					
	12					
	24					
	36					
	48					

	Mean (SE) difference from baseline to week 48					
Neutrophils (10^9/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Lymphocytes (10^9/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Monocytes (10^9/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Eosinophils (10^9/L)	0					
	4					
	8					

	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Basophils (10^9/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Potassium (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Total Protein (g/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					

Sodium (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
ALT (U/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Total bilirubin (umol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Indirect bilirubin (umol/L)	0					
	4					
	8					
	12					
	24					
	36					

	48					
	Mean (SE) difference from baseline to week 48					
AST (U/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Albumin (g/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Creatinine (umol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Creatinine clearance (mL/min)	0					

	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Alkaline phosphatase (U/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Creatinine phosphakinase (U/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Calcium (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					

	Mean (SE) difference from baseline to week 48					
Urea (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Phosphate (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Chloride (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Total cholesterol (mmol/L)	0					
	4					
	8					

	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
HDL (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
LDL (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Triglycerides (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					

Glucose (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					

The mean change in laboratory parameters from baseline to week 48 will be compared between the 2 treatment groups using a mixed model with random intercept and slope and spatial power covariance structure due to unequal time intervals between visits.

TABLE 16: CHANGE FROM BASELINE IN URINE PARAMETERS

Urine parameters	Week	**Integrase Inhibitor N=xxx**		**Protease Inhibitor N=xxx**		**P-value between groups**
Creatinine (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Glucose (mmol/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Postive/trace Glusose Dipstick, n (%)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Relative risk (RR, 95% CI) from baseline to week 48					
Proteins (mg/L)	0					
	4					
	8					
	12					

	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Albumin (mg/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Albumin : Creatinine ratio (ACR) (mg/mmoL)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Protein : Creatinine ratio (PCR) (mg/mmoL)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Phosphate (mmol/L)	0					
	4					

	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Beta-2 microglobulin (mg/L)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Mean (SE) difference from baseline to week 48					
Positive Leukocytes, n (%)	0					
	4					
	8					
	12					
	24					
	36					
	48					
	Relative risk (RR, 95% CI) from baseline to week 48					

The change in continuous urine parameters from baseline to week 48 will be compared between the 2 treatment groups using a mixed model with random intercept and slope and spatial power covariance structure due to unequal time intervals between visits.

Change in binary parameters from baseline to week 48 will be compared between the 2 treatment groups using a Generalised Estimating Equation (GEE) with independent covariance structure, binomial distribution and log link.

5. APPENDICES

APPENDIX 1 – AIDS-DEFINING CONDITIONS

From CDC, available at https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2.htm

- Bacterial infections, multiple or recurrent*
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus†
- Cervical cancer, invasive§
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision) †
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma†
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii,* disseminated or extrapulmonary†
- *Mycobacterium tuberculosis* of any site, pulmonary, †§ disseminated, † or extrapulmonary†
- *Mycobacterium*, other species or unidentified species, disseminated† or extrapulmonary†
- *Pneumocystis jirovecii* pneumonia†
- Pneumonia, recurrent†§
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month†
- Wasting syndrome attributed to HIV

* Only among children aged <13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12].)

† Condition that might be diagnosed presumptively.

§ Only among adults and adolescents aged ≥13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17].)

APPENDIX 2 - INISIGHT SERIOUS NON-AIDS EVENTS CRITERIA

Version 4, August 2012

ACUTE MYOCARDIAL INFARCTION

A. Rise and/or fall of cardiac biomarkers (preferably troponin), with at least one value above 99th percentile of upper reference limit (URL)

B. Occurrence of a compatible clinical syndrome, including symptoms (such as chest pain) consistent with myocardial ischemia

C. ECG changes indicative of new ischemia (new ST-changes or new left bundle branch block [LBBB]), or development of pathological Q waves on the ECG

D. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

E. Sudden unexpected cardiac death involving cardiac arrest before biomarkers are obtained or before a time when biomarkers appear, along with (1) new ST-changes or new LBB, or (2) evidence of fresh thrombus on coronary angiography or at autopsy

F. In patients with percutaneous coronary interventions and normal baseline troponin, increases in troponin of three times the 99th percentile of URL

G. In patients with coronary artery bypass grafting and normal baseline troponin, increases in troponin of five times the 99th percentile of URL PLUS at least one of the following: (1) new pathological Q-waves or new LBBB, (2) angiographically documented new graft or native artery occlusion, or (3) imaging evidence of new loss of viable myocardium

H. Pathologic findings of acute myocardial infarction (including acute MI demonstrated as the cause of death on autopsy)

I. Development of 1) evolving new Q waves, or 2) evolving ST elevation, preferably based on at least 2 ECGs taken during the same hospital admission

J. In patients with coronary artery bypass grafting and normal baseline troponin, increases in troponin of five times the 99th percentile of URL

Confirmed: One of the following 5 criteria (adapted from 2007 Universal Definition of Myocardial Infarction):
1. A + (B or C or D)
2. E
3. F
4. G
5. H

Probable: B+I or J

CONGESTIVE HEART FAILURE

A. Clinical signs and symptoms compatible with left or right sided heart failure (e.g., paroxysmal nocturnal dyspnea, rales or S3 on auscultation, jugular venous distention) without an alternative explanation

B. Hemodynamic measurements, radionucleotide ventriculography, echocardiogram, cardiac catheterization, or multiple gated acquisition scan showing a decreased ejection fraction of < 45%

C. Echocardiogram, cardiac catheterization or other studies showing evidence of increased left atrial pressure or right heart failure

D. Elevated levels of Brain Natriuretic Peptide (BNP) or NT-proBNP

E. Chest x-ray or other imaging study showing evidence of congestive heart failure, including cardiac enlargement

F. Documentation of treatment for congestive heart failure

Confirmed: (A+B) or (A+C) or (A+D)
Probable: A+E+F

CORONARY ARTERY DISEASE REQUIRING DRUG TREATMENT

A written report in the medical record documenting:

A. Evidence of myocardial ischemia based on either diagnostic imaging (such as a stress echocardiogram or thallium scan) or diagnostic changes on an electrocardiogram (such as during stress testing or an episode of chest pain)

B. Evidence of coronary artery disease based on coronary angiography or other diagnostic imaging

C. Other evidence of myocardial ischemia and/or coronary artery disease (including that based primarily upon symptoms and clinical presentation, such as chest pain with exertion)

D. Use of medication given to treat or prevent angina (e.g., nitrates, beta blockers, calcium channel blockers)

Confirmed: (A or B) + D
Probable: C+D

CORONARY REVASCULARIZATION

Confirmed: A procedure report, hospital discharge summary, or other medical record from the hospitalization during which the procedure was performed for treatment of coronary artery disease (including coronary artery bypass graft, coronary artery stent implant, coronary atherectomy, and percutaneous transluminal angioplasty), or a consultation note from the participant's cardiologist documenting the occurrence of the procedure

Probable: Not applicable

DECOMPENSATED LIVER DISEASE

A. Histologic, radiographic, or ultrasound evidence of cirrhosis, as documented by one of the following:
1. Histologic evidence of cirrhosis obtained by liver biopsy or autopsy
2. MRI or CT consistent with cirrhosis
3. A positive result on transient elastography (FibroScan) or other ultrasound imaging consistent with cirrhosis

B. Clinical evidence of decompensation, as documented by one of the following, and without an alternative explanation:

1. Ascites
2. Hepatic encephalopathy
3. Bleeding from gastric or esophageal varices
4. Spontaneous bacterial peritonitis

Confirmed: A+B
Probable: B

DEEP VEIN THROMBOSIS

A. Diagnosis of deep vein thrombosis (DVT) by contrast venography, helical computed tomography, MRI, or ultrasonography other comparable imaging techniques

B. An elevated D-dimer test OR abnormal plethysmography

C. A score on the Wells Clinical Prediction Rule for DVT of ≥ 3 points

D. Absence of alternative diagnosis as likely or greater than that of deep venous thrombosis

Wells Clinical Prediction Rule for DVT
One point for each of the following:

- Active cancer (treatment ongoing or within previous 6 months, or palliative)
- Paralysis, paresis, or plaster immobilization of lower extremities
- Recently bedridden for more than 3 days, or major surgery, within 4 weeks
- Localized tenderness along distribution of the deep venous system
- Entire leg swollen
- Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)
- Pitting edema (greater in the symptomatic leg)
- Collateral superficial veins (non-varicose)

(Adapted from: Wells PS et al. Lancet 1997;350:1796)

Confirmed: A
Probable: B+C+D

DIABETES MELLITUS

A. Classic symptoms of hyperglycemia or hyperglycemic crisis plus a random plasma glucose concentration >=200 mg/dl (11.1 mmol/l). (Classic symptoms include polyuria and polydipsia; Random is defined as any time of day without regard to last meal)

B. 2-hour plasma glucose >=200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water).

C. Repeated abnormal fasting plasma glucose (FPG) and/or abnormal Haemoglobin A1C level (HA1C) results using the following criteria:

1. FPG >=126 mg/dl (7.0 mmol/l) on at least two different dates (Fasting is defined as no caloric intake for at least 8 hours).

2. HA1C >=6.5% on at least two different dates
3. An FPG >=126 mg/dl (7.0 mmol/l) PLUS a HA1C >=6.5%, with these tests performed on two different dates

D. Documentation of taking an approved anti-diabetic medication to lower glucose levels in the blood, such as insulin or oral hypoglycaemic agents.

E. A single abnormal FBS OR a single abnormal HA1C

Confirmed: A or B or C
Probable: D
Possible: E

END-STAGE RENAL DISEASE

A. Haemodialysis or peritoneal dialysis documented in a clinical note for a period of at least three months

B. A kidney transplant documented in a clinical note

C. Haemodialysis or peritoneal dialysis documented in a clinical note for a period of at least one month and up to the time of death in a patient who dies within three months after dialysis begins

Confirmed: A or B
Probable: C

NON-AIDS-DEFINING CANCER

A. Diagnosis of cancer other than lymphoma, Kaposi's sarcoma (KS), or invasive cervical cancer in an autopsy report

B. Diagnosis of cancer other than lymphoma, KS, or invasive cervical cancer in a pathology report that established the diagnosis

C. Diagnosis of cancer other than lymphoma, KS, or invasive cervical cancer in a hospital discharge summary or consultation note from the hospitalization or clinic visit during which the diagnosis was established

Confirmed: A or B
Probable: C

PERIPHERAL ARTERIAL DISEASE

A. Compatible clinical signs and symptoms (e.g., intermittent claudication, femoral bruit, decreased peripheral pulses, change in colour or temperature of limb suggesting peripheral arterial disease)

B. Positive results on diagnostic imaging studies (e.g., Doppler ultrasound, contrast arteriography, MRI arteriography)

C. Ankle Brachial Pressure Index < 0.90 in non-diabetics

D. A procedure report, hospital discharge summary, or other medical record from the hospitalization during which the procedure was performed documenting an invasive procedure for treatment of peripheral arterial disease (e.g., percutaneous transluminal angioplasty, endovascular procedures, or vascular surgery), or a consultation note documenting the occurrence of the procedure

Confirmed: (A+B) or (A+C) or D
Probable: A

PULMONARY EMBOLISM

A. Symptoms compatible with pulmonary embolism, such as shortness of breath, chest pain, or haemoptysis

B. Results consistent with a diagnosis of pulmonary embolism on pulmonary angiography, helical CT, ventilation-perfusion scan or other comparable imaging studies

C. A diagnosis of pulmonary embolism on autopsy
D. Results consistent with a diagnosis of deep venous thrombosis on venography, ultrasound, or other comparable imaging studies

E. A chest x-ray which, if performed, does not suggest an alternative aetiology for the symptoms described in criteria A

Confirmed: (A+B) or C
Probable: A+D+E

STROKE

A. Acute onset with a clinically compatible course, including unequivocal objective findings of a localizing neurologic deficit

B. CT or MRI compatible with diagnosis of stroke and current neurologic signs and symptoms

C. Stroke diagnosed as cause of death at autopsy

D. Positive lumbar puncture compatible with subarachnoid haemorrhage

E. Death certificate or death note from medical record listing stroke as cause of death

Confirmed: (A+B) or C
Probable: (A+D) or (A+E)

APPENDIX 3 - INSIGHT PROGRESSION OF HIV DISEASE CRITERIA

Version 2.0, September 2010

	CONFIRMED	PROBABLE
CONSTITUTIONAL DISEASE		
HIV wasting syndrome	None	A plus B plus C: (A) unexplained, involuntary weight loss >10% from baseline, (B) persistent diarrhea with > 2 liquid stools/d for > 1 month or weakness for > 1 month or fever for > 1 month, (C) tests for alternate causes of weight loss, such as cancer, TB, MAC, cryptosporidiosis or other specific causes of weight loss, if obtained, should be negative
INFECTIONS		
Aspergillosis, invasive pulmonary	A plus B plus C: (A) CXR abnormality compatible with aspergillosis, (B) invasive mycelia consistent with Aspergillus on lung biopsy, (C) positive culture from lung biopsy or sputum collected by any method	A plus B: (A) CXR abnormality compatible with aspergillosis, (B) invasive mycelia consistent with Aspergillus on lung biopsy or positive culture of lung tissue or positive culture of sputum collected by any method
Aspergillosis, other invasive	A plus B plus C: (A) compatible clinical course, (B) invasive mycelia consistent with Aspergillus on tissue biopsy or clinical evidence of infection, (C) positive culture from the affected tissue	A plus B: (A) clinical evidence of invasive infection, (B) invasive mycelia consistent with Aspergillus on tissue biopsy or positive culture at a normally sterile site (e.g., blood) apart from the involved tissue
Bartonellosis	A plus B: (A) Clinical or histologic evidence of bacillary angiomatosis or bacillary peliosis, (B) a positive culture or PCR for *B. quintana* or *B. henselae*	A plus B: (A) Clinical evidence of bacillary angiomatosis or bacillary peliosis, (B) positive silver stain for bacilli from a skin lesion or an affected organ
Candidiasis of bronchi, trachea, or lungs	Macroscopic appearance at bronchoscopy or autopsy plus microscopic evidence of yeasts or pseudo hyphae	None
Candidiasis, esophageal	A plus B: (A) Macroscopic appearance at esophagoscopy or autopsy, (B) microscopic evidence of yeasts or pseudo hyphae	A plus B plus C: (A) Recent onset of retrosternal pain or difficulty on swallowing, (B) a clinical diagnosis of oral candidiasis, endoscopic visualization of candidiasis and/or microscopic evidence of yeasts or pseudo hyphae from oropharyngeal mucosa, (C) clinical response to treatment
	CONFIRMED	**PROBABLE**
INFECTIONS (CONTINUED)		
Chagas disease (American trypanosomiasis) of the CNS	Histologic evidence obtained by brain tissue biopsy or autopsy	A plus B plus C plus D: (A) Focal, typically hemispheral neurological

		dysfunction with onset over several days or weeks; (B) enhancing focal lesion(s) with mass effect, and surrounding edema and contrast enhancement, typically located in greymatter; (C) serum antibodies to *T. cruzi*, (D) response to standard therapy with documented clinical or radiographic improvement (if radiography was done, it must be improved), or peripheral blood smear or CSF smear positive for *T. cruzi*
Coccidioidomycosis, disseminated or extrapulmonary	From tissue other than lung or hilum, A or B or C: (A) Microscopic demonstration of spherules, (B) positive culture, (C) antigen detection	None
Cryptococcosis, meningitis or extrapulmonary	From tissue other than lung or hilum, A or B or C or D: (A) microscopic demonstration of narrow based budding yeast,) for meningitis, if done, a positive CSF India inktest,) positive culture, (D) antigen detention	None
Cryptosporidiosis	Diarrhea for > 1 month and positive microscopy	None
CMV retinitis	Autopsy demonstration	Typical appearance on fundoscopy of discrete patches of retinal whitening, spreading along blood vessels, associated with vasculitis, hemorrhage and necrosis, confirmed by ophthalmologist
CMV radiculomyelitis	Autopsy demonstration	A plus B plus C plus D plus E plus F: (A) Loss of sensation, leg weakness, or decreased reflexes, (B) presentation over 3 days to 3 weeks, (C) CT, MRI or myelogram must be done and all imaging studies must not show a mass lesion, (D) CSF shows > 10 WBC with > 50% polymorphs, (E) CSF shows no other pathogen, (F) persistence of symptoms in the absence of CMV treatment, or elevated quantitative CMV in the CSF by PCR
	CONFIRMED	**PROBABLE**
INFECTIONS (CONTINUED)		
CMV meningoencephalitis	Autopsy or brain biopsy demonstration	A plus B: (A) Rapid < 4 weeks syndrome with progressive delirium, cognitive impairment and fever, (B) CT/MRI demonstration of periventricular abnormalities or elevated quantitative CMV DNA in the CSF by PCR
CMV, other disease	A plus B plus C plus D: (A) compatible illness, (B) histologic demonstration of inclusion bodies from affected tissue, (C) if done, detectible CMV antibodies, (D) if done, detectible CMV DNA or	A plus B plus C plus D: (A) Compatible illness, (B) moderate to markedly high CMV antigen or CMV DNA in blood, (C) response to therapy, (D) if done, detectible CMV

	CMV antigen in blood	antibodies
HSV mucocutaneous ulceration	A plus B: (A) Ulceration for > 1 month, (B) histology, culture, PCR, or detection of antigen from affected tissue	A plus B: (A) Typical HSV ulceration for > 1 month, (B) response to an antiviral active against HZV unless resistance is demonstrated
HSV, bronchitis, pneumonitis, esophagitis, or other visceral disease	A plus B: (A) Compatible symptoms, (B) histology, culture, PCR, or detection of antigen from affected tissue	None
HZV, disseminated	A plus B: (A) multiple ulcerated lesions affecting at least 2 non-contiguous dermatomes, or with generalized cutaneous dissemination; or HZV involvement of the lung, liver, brain, or other internal organs (B) positive culture, PCR, or antigen assay from affected tissue	A plus B: (A) multiple typical ulcerated lesions affecting at least 2 non-contiguous dermatomes, or with generalized cutaneous dissemination (B) response to an antiviral active against HZV unless resistance is demonstrated
Histoplasmosis, disseminated or extrapulmonary	A plus B: (A) Compatible symptoms, (B) histology or culture or elevated blood or urine antigen levels	None
Isosporiasis	Diarrhea for > 1 month, plus microscopic identification of *Isospora belli*	None
Leishmaniasis, visceral	Compatible symptoms, plus microscopic identification of Leishmania	Compatible symptoms, plus a positive PCR test for Leishmania
Microsporidiosis	Diarrhea for > 1 month plus Microscopic identification of Microsporidia	None
	CONFIRMED	**PROBABLE**
INFECTIONS (CONTINUED)		
MAC and other mycobacterial disseminated disease	A plus B: (A) Fever, fatigue, anemia or diarrhea, (B) positive culture from blood, body fluids or tissue other than pulmonary, hilar or stool	A plus B plus C: (A) Fever, fatigue, anemia or diarrhea, (B) AFB or positive direct MAC PCR in blood, body fluids or tissue other than pulmonary, hilar or stool (C) no concurrent non-pulmonary TB
M. tuberculosis disease, pulmonary	A plus B: (A) Compatible symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) culture or PCR from sputum or bronchial lavage or lung tissue	A plus B plus C plus D: (A) Symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) abnormal chest X-ray, (C) AFBs seen in sputum or lavage or lung tissue but not grown in culture, (D) responds to treatment **POSSIBLE (pulmonary TB only)** A plus B plus C plus D: (A) Symptoms of fever, dyspnea, cough, weight loss or fatigue, (B) abnormal chest X-ray compatible with pulmonary TB (such as upper lobe cavitation, pleural exudate), (C) No other etiology for pulmonary symptoms and signs identified, (D) Responds to anti-tuberculosis treatment
M. tuberculosis disease, extrapulmonary	A plus B: (A) Compatible symptoms, (B) culture or PCR from blood or affected tissue	A plus B plus C: (A) Compatible symptoms, (B) AFBs seen from affected tissue or blood (C) concurrent diagnosis of pulmonary TB or responds to treatment
Nocardiosis	Clinical evidence of invasive infection	Clinical evidence of invasive

	plus a positive culture from the affected tissue or blood	infection plus microscopic evidence of bronchial weakly acid-fast organisms from the affected tissue
Penicillium marneffei, disseminated	Culture from a non-pulmonary site	Known presence in a *P. marneffei* endemic area plus characteristic skin lesions plus response to antifungal therapy for penicillosis
	CONFIRMED	**PROBABLE**
INFECTIONS (CONTINUED)		
PcP	A plus B: (A) compatible clinical syndrome, (B) microscopic or histological demonstration of *P. jirovecii* cysts in a pulmonary specimen	A plus B plus C plus D plus E: (A) dyspnea or cough, or fever progressive over > 1 week, (B) diffuse chest x-ray abnormality or, if on inhalational pentamidine, diffuse upper lung field abnormality, (C) evidence of hypoxia, (D) not suggestive of bacterial pneumonia (i.e., not purulent sputum or hemoptysis, no bacterial pathogen identified in blood or bronchial wash), (E) response to PcP treatment
Pneumocystis jirovecii, extrapulmonary	Compatible symptoms, plus microscopy	None
Pneumonia, recurrent bacterial, excludes: (a) post- obstructive pneumonias, including in those with intrapulmonary/bronchial lesions, (b) aspiration pneumonia, including in those with decreased consciousness levels, (c) nosocomial ventilator-associated pneumonias	Both pneumonia episodes must occur after enrollment and satisfy criteria (A) plus (B) plus (C). The recurrent pneumonia must also satisfy criteria (D) plus (E): (A) Signs and symptoms suggestive of bacterial pneumonia, (B) focal CXR abnormality compatible with bacterial pneumonia, (C) identification of a bacterial pathogen by positive blood culture, positive bronchoscopic sputum culture, detection of Legionella or pneumococcal antigen in urine or blood or diagnostic serologic findings, (D) the second pneumonia had onset of symptoms < 365 days after the first episode, (E) there is strong evidence that the first episode was cured such as an intervening clear CXR or absence of symptoms after > 1 month off antibacterials effective against pathogens commonly producing pneumonia	Both pneumonia episodes must occur after enrollment and satisfy criteria (A) plus (B). The recurrent pneumonia must also satisfy criteria (C) plus (D): (A) Signs and symptoms suggestive of bacterial pneumonia, (B) focal CXR abnormality compatible with bacterial pneumonia, (C) the second pneumonia had onset of symptoms < 365 days after the first episode, (D) there is strong evidence that the first episode was cured such as an intervening clear CXR or absence of symptoms after > 1 month off antibacterials effective against pathogens commonly producing pneumonia
PML (progressive multifocal leukoencephalopathy)	A or B: (A) positive histology, (B) compatible clinical and radiologic course and positive CSF PCR for JK virus	A plus B plus C: (A) Consistent symptoms, (B) brain image consistent with PML, (C) no response to toxo treatment or toxoplasma seronegative
	CONFIRMED	**PROBABLE**
INFECTIONS (CONTINUED)		
Rhodococcus equi disease	Clinical evidence of invasive infection plus microbiologic identification of the organism in the affected tissue or blood	None
Salmonella septicemia, recurrent	Both episodes must occur after enrollment and met criterion (A). The second episode must meet criteria (B)	None

	and C: (A) Positive blood or tissue culture, (B) the second septicemia had onset of symptoms < 365 days after the first episode, (C) the second septicemia must be due to a different Salmonella serotype or there must be strong evidence that the first episode was cured such as a negative blood culture off effective antibacterials for > 1 week or absence of symptoms off antibacterials for > 1 month	
Toxoplasmosis of brain	Microscopy	A plus B plus C: (A) Symptoms of focal intracranial abnormality or decreased consciousness, (B) brain image consistent with lesion(s) enhanced by contrast, (C) positive toxoplasma serology or responds to treatment clinically or by scan
NEOPLASMS		
Cervical carcinoma, invasive	Histology (NOT carcinoma-in- situ)	None
Kaposi sarcoma, (mucocutaneous or visceral)	Histology	Highly typical appearance and persistence for > 1 month
Lymphoma, primary, of brain	Histology	Symptoms consistent with lymphoma plus at least one CNS lesion with mass effect plus lack of clinical and radiographic response to at least 2 weeks of treatment for toxoplasmosis
Lymphoma, Hodgkin's	Histology	None
Lymphoma, non-Hodgkin's, all cell types	Histology	None
	CONFIRMED	**PROBABLE**
NEUROLOGICAL		
HIV-related encephalopathy (including AIDS Dementia Complex)	None	Cognitive or motor dysfunction interfering with usual activity, progressive over weeks or months plus no other condition to explain the findings plus brain image obtained and suggests no other causes plus grade 2 or worse impairment in at least 2 domains by NARS (see below) excluding abnormal domains at trial entry. (For persons with abnormal domains at entry worsening by at least two grades meets criteria.)

Abbreviated NARS (Neuropsychiatric AIDS Rating Scale) Grading for HIV Encephalopathy

Adapted from: Price RW, Brew BJ. The AIDS dementia complex. J Infect Dis 1988; 158 (5): 1079- 83, and Hughes CP, Berg L, Danziger WL. A new clinical scale for the staging of dementia. Brit J Psych 1982; 140: 566-92.

NARS stage	Cognitive-Behavioral Domains					
	Orientation	**Memory**	**Motor**	**Behavior**	**Problem solving**	**Activities of daily living**
0.5	fully oriented	complains of memory problems	fully ambulatory slightly slowed movements	normal	has slight mental slowing	slight impairment in business dealings
1	fully oriented, may have brief periods of “spaciness"	mild memory problems	balance, co-ordination and handwriting difficulties	more irritable, labile or apathetic, withdrawn	difficulty planning and completing work	can do simple daily tasks, may need prompting
2	some disorientation	memory moderately impaired, new learning impaired	ambulatory but may require walking aid	some impulsivity or agitated behavior	severe impairment, poor social judgement, gets lost easily	needs assistance with ADLs
3	frequent disorientation	severe memory loss, only fragments of memory remain	ambulatory with assistance	may have organic psychosis	judgement very poor	cannot live independently
4	confused and disoriented	virtually no memory	bedridden	mute and unresponsive	no problem-solving ability	nearly vegetative

APPENDIX 4 – IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME GENERIC CRITERIA

(Revised 01/10/09)
From ACTG, available under https://actgnetwork.org/IRIS_Case_Definitions

1. **Initiation, reintroduction or change in antiretroviral therapy/regimen or therapy for opportunistic infections (OI).**

   AND

2. **[1]Evidence of:**
   a. **an increase in CD4+ cell count as defined by ≥50 cells/mm^3 or a ≥2- fold rise in CD4+ cell count, and/or**
   b. **decrease in the HIV-1 viral load of >0.5 log10 and/or**
   c. **weight gain or other investigator-defined signs of clinical improvement in response to initiation, reintroduction or change of either antiretroviral therapy/regimen or OI therapy.**

   AND

3. **Symptoms and/or signs that are consistent with an infectious or inflammatory condition.**

   AND

4. **These symptoms and/or signs cannot be explained by a newly acquired infection, the expected clinical course of a previously recognized infectious agent, or the side effects of medications.**

   AND

5. **For purposes of data collection, the infectious/inflammatory condition must be attributable to a specific pathogen or condition. A Clinical Events form should be completed 16 weeks (± 4 weeks) after initial report if diagnosis confirmed or changed from initial report**

[1] If the study participant is being evaluated for an inflammatory condition at a time that is <4 weeks after initiation, reintroduction or change in antiretroviral therapy/regimen or OI therapy, items 2a through 2c are not required.

Refer to the "Criteria for the Diagnosis of Specific Immune Reconstitution Inflammatory Syndromes (IRIS)" document for specific Opportunistic Infection (OI) and non-pathogen condition diagnosis criteria.

Criteria for the Diagnosis of Specific Immune Reconstitution Inflammatory Syndromes (IRIS)

IRIS Focus Group

Given the paucity of data for a clearly-defined immune reconstitution inflammatory syndrome for each opportunistic pathogen, the IRIS Working Group concentrated on developing specific definitions for the most well-characterized IRIS in the literature. IRIS events may occur as paradoxical worsening or as an unmasking. Paradoxical responses are described as an initial clinical worsening when patients are started on pathogen-specific therapy and/or ART simultaneously. Unmasking refers to aberrant clinical presentations of previously common OIs such as localized Mycobacterium avium *complex (MAC) lymphadenitis and* Cytomegalovirus *(CMV) vitritis occurring within the first weeks of starting ART suggesting that patients have sub-clinical disease prior to the initiation of ART. There are specific definitions including confirmed and probable for the following specific pathogen IRIS:* Mycobacterium avium *complex (MAC),* Progressive Multifocal Leukoencephalopathy *(PML),* Cytomegalovirus *(CMV),* Mycobacterium tuberculosis *(TB) and* Cryptococcus neoformans*. All other clinical syndromes attributed to immune reconstitution will be treated as probable IRIS events without specific definitions and will include* Pneumocystis jirovecii *pneumonia (PCP), Varicella Zoster (VZV), Herpes Simplex (HSV), Hepatitis B, Hepatitis C, Toxoplasmosis, Kaposi's Sarcoma, Graves' disease, Sarcoidosis, and other autoimmune disorders. For these less well-defined IRIS, key data will be captured on a generic form that includes clinical signs/symptoms, CD4, HIV RNA data, and clinical outcomes.*

Specific IRIS Case Definitions

1. ***Cytomegalovirus*** **(CMV):** ***{Ophthalmologic only}*** IRIS associated with CMV is fairly common; syndromes include uveitis, vitritis, extension or new development of retinal opacification, proliferative vitreoretinopathy (leading to retinal detachment), neovascularization, macular or optic nerve edema and subcapsular cataracts (leading to visual impairment) [1, 2]. The inflammatory component is marked, with significant anterior and/or posterior chamber inflammation. Vitritis and extension or new development of retinal opacification usually occurs within 3-12 weeks of beginning antiretroviral therapy/regimen and/or CMV antiviral therapy; uveitis may occur months to years after beginning antiretroviral therapy. Antiretroviral therapy/regimen is usually continued; some patients are also treated with anti-CMV drugs, especially those with sight-threatening disease. IRIS associated with gastrointestinal or neurologic (non-ocular) CMV disease have not be adequately characterized

   Confirmed CMV IRIS in patients *with* a prior history of CMV retinitis: previous CMV retinitis diagnosis by ACTG criteria and improvement of signs/symptoms with anti-CMV therapy, with the subsequent development of ocular inflammatory changes in uveovitreal tract, lens or retina, with or without associated visual changes, as documented by an experienced ophthalmologist.

   Confirmed CMV IRIS in patients *without* a prior history of CMV retinitis: the development of significant ocular inflammation in the uveovitreal tract, lens or retina attributed to CMV in the absence of ophthalmologic findings typical for acute CMV retinitis, with or without visual changes, as documented by an experienced ophthalmologist.

   Probable **CMV IRIS in patients *with* a prior history of CMV retinitis** previous CMV retinitis diagnosis by ACTG criteria and improvement of signs/symptoms with anti-CMV therapy, with the subsequent development of ocular inflammatory changes in uveovitreal tract, lens or retina, with or without associated visual changes, as documented by a non-ophthalmologist clinician

2. ***Cryptococcus neoformans***. The best described cases of *Cryptococcus neoformans* IRIS involve inflammatory changes developing in patients with recently diagnosed cryptococcal meningitis, cryptococcemia or pneumonia who have responded to appropriate antifungal therapy [1, 3,4]. Most have presented as meningitis, associated with CSF abnormalities (significantly elevated protein, lymphocytes, hypoglycorrhachia and cryptococcal antigen titers) with negative cultures. CNS imaging may demonstrate new meningeal inflammation. Significant elevations of intracranial pressure may occur. Non-CNS presentations are also common and have included the development of mediastinal or cervical adenopathy, necrotizing pneumonia, cavitation of previously documented pulmonary lesions, focal lymphadenitis and cutaneous abscesses. Biopsies may demonstrate granulomatous changes and cryptococci but typically cultures are negative. These presentations have occurred anywhere from two weeks to 11 months after initiation of antiretroviral therapy/regimen, with most cases occurring within three months. Less well described are cases of cryptococcal meningitis presenting only after initiation and response to antiretroviral therapy/regimen, also associated with elevated CSF cryptococcal antigen (CRAG) titers, negative CSF cultures and significant meningeal enhancement on scan.

   Confirmed cryptococcal IRIS in patients *with* a prior history of cryptococcosis: Cryptococcal meningitis or other diagnosis of systemic cryptococcal infection (fungemia, pneumonia) by ACTG criteria and improvement of signs/symptoms with antifungal therapy, with the subsequent development of new or worsening pulmonary infiltrates, new meningeal enhancement on scan or abnormal CSF findings (low glucose, elevated WBC, CSF CRAG with negative fungal culture), mediastinal or cervical lymphadenopathy, pleural effusion, cutaneous abscesses or cryptococcal lesions at other sites; histopathology from non-meningeal site demonstrating inflammatory changes and organisms in the absence of a positive culture or positive culture.

   Confirmed cryptococcal IRIS in patients *without* a prior history of cryptococcosis: the development of meningitis with meningeal enhancement on scan with abnormal CSF findings (low glucose, elevated WBC, positive CSF CRAG with negative or positive fungal culture), mediastinal or cervical lymphadenopathy, pleural effusion, cutaneous abscesses or cryptococcal lesions at other sites; histopathology from non-meningeal site demonstrating inflammatory changes and organisms in the absence of a positive culture or positive culture.

   Probable cryptococcal IRIS in patients* with *a prior diagnosis of cryptococcosis: *previous cryptococcosis diagnosis by ACTG criteria and improvement of signs/symptoms with anti-cryptococcal therapy, and the subsequent development of focal inflammatory site(s); histopathology from involved site or sterile body fluid analysis demonstrating inflammatory changes (e.g., granulomas, lymphocytes) in the absence of positive stains or cultures for any other pathogen or any non-infectious histopathologic diagnosis; and negative blood cultures for Cryptococcosis; and negative CSF CRAG if obtained or development of new onset CNS signs or symptoms with meningeal enhancement or other atypical radiographic changes with no evidence of other neurologic disease to explain the findings.*

   Probable cryptococcal IRIS in patients* without *a prior diagnosis of cryptococcosis: *the subsequent development of focal inflammatory site(s); histopathology from involved site or sterile body fluid analysis demonstrating inflammatory changes (e.g., granulomas, lymphocytes) accompanied by evidence consistent with cryptococcosis in the absence of positive cultures for any other pathogen.*

3. ***Mycobacterium avium* complex (MAC).** This is one of the best described IRIS. The most common presentation is focal lymphadenitis (especially cervical) with high fever, elevated WBC counts and negative blood cultures; fistula formation may occur. There is a significant inflammatory

component on biopsy with necrotizing granulomas, caseation and AFB. The syndrome usually occurs within 3-12 weeks of initiating antiretroviral therapy/regimen and/or anti-mycobacterial therapy**,** although rare cases have been described beyond 6 months with deep tissue foci, e.g. psoas abscess. MAC IRIS has presented as diffuse adenopathy, and as focal disease in diverse sites (paraspinous, mediastinal, abdominal, vertebral, pulmonary and CNS). [1,5,6]

Confirmed MAC IRIS in patients *with* a prior history of disseminated MAC (dMAC): previous disseminated MAC diagnosis by ACTG criteria and improvement of signs/symptoms with anti-MAC therapy, with the subsequent development of focal inflammatory site(s).

Confirmed MAC IRIS in patients *without* a prior history of dMAC: the development of focal inflammatory site(s); histopathology from the involved site demonstrating inflammatory changes (e.g., granulomas) accompanied by histologic or culture evidence of AFB consistent with MAC in the absence of positive cultures for any other AFB; and may have positive blood cultures for MAC.

Probable MAC IRIS in patients *with* a prior history of dMAC: previous dMAC diagnosis by ACTG criteria and improvement of signs/symptoms with anti-MAC therapy, and the subsequent development of focal inflammatory site(s); histopathology from involved site demonstrating inflammatory changes (e.g., granulomas) in the absence of positive stains or cultures for any other pathogen or any non-infectious histopathologic diagnosis; and negative blood cultures for MAC.

Probable MAC IRIS in patients *without* a prior diagnosis of MAC: the subsequent development of focal inflammatory site(s); histopathology from involved site demonstrating inflammatory changes (e.g., granulomas, lymphocytic infiltrates) and without evidence of any other specific pathogen (stains may be positive for AFB); and negative blood cultures for MAC.

4. ***Mycobacterium tuberculosis* (TB).** Tuberculosis-associated IRIS can present as one of two main syndromes: (1) a paradoxical reaction after the start of ART in patients receiving tuberculosis treatment ("paradoxical" tuberculosis-associated IRIS), or (2) a new presentation of tuberculosis that is "unmasked" in the weeks following initiation of ART with an exaggerated inflammatory clinical presentation or complicated by a paradoxical response ("unmasking" tuberculosis associated IRIS). A "paradoxical" response to anti-tuberculous therapy was described as far back as 1955 in patients initiating therapy. In the HAART era, IRIS associated with TB is common and occurs in approximately 8-43% and typically consists of new and persistent fever after starting antiretroviral therapy/regimen; worsening or emergence of intrathoracic adenopathy, pulmonary infiltrates or pleural effusions, *or* worsening or emergence of cervical nodes on serial exam or of other tuberculous lesions, such as skin and CNS. It usually occurs within the first 4 weeks of beginning antimycobacterial therapy with or without antiretroviral therapy/regimen but has been described as late as 9 months when the patient is smear-negative. Antiretroviral therapy/regimen can usually be continued, often with anti-inflammatory support; corticosteroids have been used in those with CNS lesions or who are critically ill [7-12].

Confirmed TB IRIS in patients *with* a prior history of TB (paradoxical TB-associated IRIS): There are three components to this case-definition (adopted from Lancet Infect Dis 2008, reference 12):

A) Antecedent requirements

i) Diagnosis of tuberculosis: previous pulmonary (smear positive or smear-negative) or extrapulmonary TB diagnosis by ACTG criteria

AND

ii) Initial response with anti-TB therapy (i.e. stabilization or improvement of signs/symptoms with appropriate anti-TB therapy prior to initiation of ART)*. For example, there has been cessation or improvement of fevers, cough, night sweats).

* (Note: this does not apply to patients starting ART within 2 weeks of starting tuberculosis treatment since insufficient time may have elapsed for a clinical response to be reported)

(B) Clinical criteria

The onset of tuberculosis-associated IRIS manifestations should be within 3 months of ART initiation, re-initiation, or regimen change because of HIV treatment failure.

Of the following, at least one major criterion or two minor clinical criteria are required:

Major criteria

• New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement—e.g. tuberculous arthritis

• New or worsening radiological features of tuberculosis (found by chest radiography, abdominal ultrasonography, CT, or MRI)

• New or worsening CNS tuberculosis (meningitis or focal neurological deficit; e.g. caused by tuberculoma)

• New or worsening serositis (pleural effusion, ascites, or pericardial effusion)

Minor criteria

• New or worsening constitutional symptoms such as fever, night sweats, or weight loss

• New or worsening respiratory symptoms such as cough, dyspnea, or stridor

• New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) Alternative explanations for clinical deterioration must be excluded

• Failure of tuberculosis treatment because of tuberculosis drug resistance

• Poor adherence to tuberculosis treatment

• Another opportunistic infection or neoplasm (it is particularly important to exclude an alternative diagnosis in patients with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis where the initial tuberculosis diagnosis has not been microbiologically confirmed)

• Drug toxicity or reaction

Confirmed TB IRIS in patients *without* a prior history of TB (ART "unmasking" TB-associated IRIS): Patient is not receiving treatment for TB when ART is initiated. Active TB is diagnosed after initiation of ART and the diagnosis of TB fulfils ACTG criteria for smear-positive pulmonary TB, smear-negative pulmonary TB or extrapulmonary TB. Active TB develops within 3 months of

starting ART and one of the following criteria is met: heightened intensity of clinical manifestations, particularly if there is evidence of a marked inflammatory component. For example, presentations may include TB lymphadenitis or TB abscesses with prominent acute inflammatory features; the development of pulmonary* or extrapulmonary TB with no evidence of miliary disease accompanied by marked focal inflammation; or histopathology from involved site demonstrating inflammatory changes (e.g., granulomas, caseation) accompanied by histologic or culture evidence of AFB consistent with TB in the absence of positive cultures for any other AFB.

Probable TB IRIS in patients *with* a prior history of TB: "Probable" status should be assigned for cases where criteria A and B are met (see confirmed TB IRIS with a prior history of TB definition) but an alternative diagnosis or explanation for clinical deterioration cannot be fully excluded.

Probable TB IRIS in patients *without* a prior diagnosis of TB: Patient is not receiving treatment for TB when ART is initiated. Active TB is diagnosed after initiation of ART and the diagnosis of TB fulfils ACTG criteria for smear-positive pulmonary TB, smear-negative pulmonary TB or extrapulmonary TB. There is heightened intensity of clinical manifestations but there is not clear evidence of a marked inflammatory component to the presentation or the subsequent development of focal inflammatory site(s) is beyond 3 months of ART initiation.

5. ***Progressive Multifocal Leukoencephalopathy*** **(PML)**. Inflammatory responses to PML usually occur within 3 months of beginning antiretroviral therapy. Based on available data, the simultaneous diagnosis of PML and IRIS post-HAART initiation is more commonly observed (i.e. unmasking IRIS). Furthermore, it appears that paradoxical worsening PML IRIS is identified sooner (within 4 weeks) than unmasking PML IRIS. MRI with gadolinium shows contrast enhancement suggesting an inflammatory response, and biopsy reveals significant inflammation with gliosis, marked intraparenchymal and perivascular infiltration by macrophages and lymphocytic infiltrates (especially CD8 T cells), giant cells, with or without demyelination. Intense JC-specific PCR signals (or other immunoreactivity to papovavirus antigens) are detected in brain tissue even in the absence of positive JC CSF PCR. The clinical responses are mixed: some improve, and some have significant worsening with progression to death. A variable response to steroids has been described [1,13,14].

   Confirmed PML IRIS in patients *with* a prior history of PML: previous PML diagnosis by ACTG criteria (consistent CT or MRI scan with positive biopsy or positive CSF JC PCR and the absence of any alternative diagnosis), with the subsequent development of new or worsening CT or MRI findings with contrast enhancement; brain biopsy shows focal inflammatory changes accompanied by histologic or PCR evidence of PML in the absence of another diagnosis.

   Confirmed PML IRIS in patients *without* a prior diagnosis of PML: the development of new neurologic deficit(s) in patient with no previously recognized CNS infection or malignancy, accompanied by CT or MRI changes showing contrast enhancement; brain biopsy shows focal inflammatory changes accompanied by histologic or PCR evidence of PML in the absence of another diagnosis.

   Probable PML IRIS in patients *with* a prior history of PML: previous PML diagnosis by ACTG criteria (consistent CT or MRI scan with positive biopsy or CSF JC PCR and the absence of any alternative diagnosis), with the subsequent development of new or worsening CT or MRI findings with contrast in the absence of another diagnosis.

Probable PML IRIS in patients *without* a prior diagnosis of PML: the development of new neurologic deficit(s) in a patient with no previously recognized CNS infection or malignancy accompanied by CT or MRI changes showing contrast enhancement consistent with PML with no brain biopsy obtained. CSF findings cannot be attributable to another pathogen or disease process.

IRIS Diagnoses without Specific Case Definitions

Pathogen-Directed:

1. ***Kaposi's Sarcoma* (KS*).*** Rapid KS progression [15] and local swelling with adjacent lymphadenopathy [20] have both been reported as a manifestation of immune reconstitution after antiretroviral therapy/regimen initiation. Whereas the latter syndrome may truly represent an IRIS syndrome, if there is no clear evidence of any characteristic inflammatory component [1, 16], then the progression could be due to a failure to reconstitute KSHV-specific immune responses. KS-IRIS is defined as a sudden or more dramatic progression of disease than expected as part of natural history that occurs within 12 weeks of initiation of ART. ART alone should be continued for 4-6 weeks to monitor for clinical response. If the lesions stabilize, have a regression of inflammation or lesion number or size diminishes, this will be defined as IRIS. Should disease progression continue, then this is unlikely to be IRIS and should be defined as progression of disease and managed with appropriate KSHV specific therapies. The presence of inflammation on biopsy may assist in distinguishing progression of disease vs. IRIS.

2. **Hepatitis B and C.** *Significant increase in ALT over baseline (flares) have been documented after beginning antiretroviral therapy/regimen with HBV co-infection as well as after interruption of antiretroviral therapy/regimen (especially in patients with HBV on a 3TC- or tenofovir-containing regimen). After immune recovery HBV "flares" may occur if HBV is not being concomitantly treated, although there are other potential reasons to consider. These include:*

   a) spontaneous HBeAg seroconversion;
   b) treatment induced exacerbation of the underlying disease;
   c) hepatotoxic effects of treatment;
   d) withdrawal of active HBV drug;
   e) development of resistance and return of replication, and/or
   f) superimposed and unrelated acute liver disease (e.g. hepatitis A)

   Liver biopsy may be helpful in determining evidence of drug related (eosinophilic infiltrate) vs. acute viral hepatitis (hepatocyte swelling with lobular inflammation).

   Biopsy may also grade and stage chronic viral hepatitis. IRIS is less well-defined in HCV co-infection, and increases in liver enzymes on antiretroviral therapy/regimen may be multifactorial as well.

3. **Herpes simplex virus *(HSV).*** *The development of unusual presentations of HSV following the initiation of antiretroviral therapy/regimen attributed to immune reconstitution have been rarely described.*

Localized HSV vesicles may occur within 8 weeks of initiating ART among persons with no prior history and no new source contact to attribute it to. Symptoms and signs are frequently consistent with a primary infection. Chronic erosive or ulcerative lesions of the genitals have been described in individuals who had prior histories of genital HSV. The appearance and clinical course of the lesions attributed to immune reconstitution appeared inconsistent with these patients' previous HSV presentations. Proctitis has also been reported [1,18,19]. Routine viral cultures may or may not yield HSV though histochemistry studies may show evidence of HSV antigens in the absence of a positive viral culture. Histopathology in some cases may demonstrate an inflammatory infiltrate with unusual prominence of plasma cells and eosinophils. Response to antivirals appears to be variable.

4. ***Pneumocystis jirovecii pneumonia* (PCP).** Despite being the most common OI with a relatively high CD4 threshold for development, few clear cases of Pneumocystis pneumonia IRIS have been documented so far (likely because steroids have been established for the use of severe PCP). Cases have been described as worsening of pneumonia and even respiratory failure, although the patients reported received suboptimal courses of steroids [20]. To entertain a diagnosis of PCP IRIS, bronchoscopy should rule out an intercurrent pulmonary process.

5. **Syphilis*.*** *New reactive RPR within 12 weeks of starting ART in setting of known previously treated syphilis and documented nonreactive within past 2 years without new attributable source. May also present serologically as less than or equal to 4-fold change in titer in someone with previous history of treated syphilis and no new attributable source. May present with systemic symptoms including arthralgia. May improve with anti-inflammatories.*

1.

6. ***Toxoplasmosis*.** There is also a very small database for possible toxoplasmosis IRIS. No specific clinical pattern has been seen, and there is no clear evidence of an inflammatory component.

7. ***Varicella Zoster* (VZV).** The development of herpes zoster after initiation of antiretroviral therapy/regimen has been attributed to immune reconstitution. The incidence of zoster appears to be 2- to 5-fold greater in those receiving antiretroviral therapy/regimen compared to those not receiving antiretroviral therapy/regimen. Most cases occur in the first 16 weeks following initiation of antiretroviral therapy/regimen. Those with higher percentage of CD8+ lymphocytes at the time of initiation of HAART and at one month following antiretroviral therapy/regimen appeared to be at higher risk for zoster [21]. Most cases present as cutaneous dermatomal disease or mucocutaneous disease, are mild, occur without systemic symptoms and respond to antiviral therapy. Iritis and keratitis have been described rarely [1,22]. It is not clear that cutaneous zoster following initiation of antiretroviral therapy/regimen has a significant inflammatory component that differentiates this from routine VZV.

8. **Other viral dermatose**s. Eruptive onset of new common warts, flat warts, or epidermodysplasia verruciformis-type warts, or inflammation/rapid growth of previously stable cutaneous or genital warts, have been noted during immune restoration [23-24]. In addition, eruptive onset of new molluscum contagiosum or inflammation/enlargement of pre-existing mollusca during immune restoration has been described [25].

Non-Pathogen or Unknown Pathogen Directed

1. ***Autoimmune disorders*.** Systemic lupus erythematosus, polymyositis, rheumatoid arthritis, relapsing polychondritis and Guillain-Barre have also been attributed to immune reconstitution following administration of antiretroviral therapy/regimen [1,26].

2. ***Follicular inflammatory eruptions***. Sudden onset of follicular papulopustular inflammatory eruptions resembling acne vulgaris or acne rosacea have been reported within first 4 months of immune reconstitution [27]. Eosinophilic folliculitis, distinguished from acneiform eruptions by intense pruritus, an urticarial appearance to the papules, and histopathology showing follicular inflammation containing eosinophils, has been documented. An increased incidence of eosinophilic folliculitis has been noted in the first 6 months of HAART therapy [28].

3. ***Graves' Disease***. New onset of clinically significant Graves' disease (hyperthyroidism) has been reported following the initiation of antiretroviral therapy/regimen. The development of anti-thyrotropin receptor antibodies in individuals following antiretroviral therapy/regimen, not present before antiretroviral therapy/regimen initiation has been described [1, 26].

4. **Sarcoidosis.** *Worsening of previously diagnosed sarcoidosis or newly diagnosed sarcoidosis following antiretroviral therapy/regimen has been reported. Pulmonary involvement as well as extrapulmonary involvement (erythema nodosum) has been described [1, 26].*