HIV-1 & Coronavirus-Coinfection in Europe: Morbidity & Risk Factors of COVID-19 in People Living With HIV

NCT: NCT05481216

Date: 29 August 2022

HIV-1 & Coronavirus-Coinfection in Europe: Morbidity & Risk Factors of COVID-19 in People Living With HIV

- HIV CoCo -

Version 3.0 dated 29 August 2022

Sponsor Protocol ID: 303CoCo

SPONSOR: NEAT ID - The European treatment network of HIV, hepatitis and global infectious diseases

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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 study in compliance with the approved protocol and will adhere to the principles outlined in the ISPE guidelines of Good Pharmacoepidemiology Practice (GPP) and Heads of Medicines Agencies (HMA), the GDPR and other applicable Data Protection legislation, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as applicable or 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 study Sponsor:

Signature:
..... Date: ...../...../.....

Name: (please print):
.....

Chief Investigator:

Signature:
..... Date: ...../...../.....

Name: (please 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 study in compliance with the approved protocol, Statistical Principles for Clinical Trials, ICH E10 and will adhere to the principles outlined in the ISPE guidelines of Good Pharmacoepidemiology Practice (GPP) and Heads of Medicines Agencies (HMA), the GDPR and other applicable Data Protection legislation, GCP guidelines, the Sponsor's SOPs and other regulatory requirements as applicable or 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: (please print):
.....

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study in accordance with principles outlined in the ISPE guidelines of Good Pharmacoepidemiology Practice (GPP) and Heads of Medicines Agencies (HMA), the GDPR and other applicable Data Protection legislation, ICH-GCP 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 study related essential documentation for the duration of the study as necessary.

Principal Investigator:

Signature:
..... Date: ...../...../.....

Name: (please print):
.....

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STUDY SYNOPSIS

Full study Title	**HIV**-1 & **Co**ronavirus-**Co**infection in Europe: Morbidity & Risk Factors of COVID-19 in People Living With HIV (PLWHIV)
Short title/Acronym	HIV CoCo
Clinical Phase	Observational Study
Study Design	Retrospective, case-control study
Study Population & Planned Sample Size	**Cases:** 500 PLWHIV with COVID-19 **Controls:** 1,000 PLWHIV without COVID-19 & upto 1500 HIV seronegative COVID-19 patients
Eligibility Criteria	**Cases:** at least 18 years of age with documented HIV-1 infection and confirmed SARS-CoV-2 infection by documented, or patient-reported, positive result on PCR testing of a nasopharyngeal or respiratory sample, before 1st April 2021. **Controls:** at least 18 years of age with either: documented HIV-1 infection; or confirmed SARS-CoV-2 infection by documented, or patient-reported, positive result on PCR testing of a nasopharyngeal or respiratory sample, before 1st April 2021. Controls must also meet the matching criteria.
Indication	HIV & COVID-19
Methodology	Only real-world retrospective data will be used for this study. Deidentified retrospective data will be transcribed into the eCRF system from source data at each clinical site or from existing COVID-19 cohort databases, where appropriate. No personal identifiable data will be transmitted to NEAT ID. Each case will be matched to control as per the criteria set out below: For comparing PLWHIV & COVID-19 versus HIV seronegative COVID-19 patients, a 1:1 or 1:3 matching will be performed according to the following criteria: • Age (+/- 5 years) • Sex • Ethnicity (where available) • Month of COVID-19 diagnosis (+/- 2 months) • COVID-19 diagnosis inpatient, 1:1 matching OR • COVID-19 diagnosis outpatient (ambulatory), 1:3 matching For comparing PLWHIV & COVID-19 versus PLWHIV without COVID-19, a 1:2 matching for similar risk of acquiring COVID-19 will be performed according to the following criteria: • Age (+/- 5 years) • Sex • Ethnicity (where available)
Number of sites	Up to 30 sites

Objectives	**Primary** 1. To describe outcomes of COVID-19 in PLWHIV in comparison to HIV seronegative COVID-19 controls. 2. To identify risk factors (e.g. CD4 cell nadir, current CD4 count, co-morbidities) for severe COVID-19 outcomes within the group of PLWHIV.	**Secondary** 1. To describe differences in the clinical manifestation of COVID-19 in PLWHIV as compared to HIV seronegative controls. 2. To describe the response to treatment, including supportive care and novel therapeutics against COVID-19, including antiviral or immunomodulatory therapy 3. To describe the co-morbidities in PLWHIV and controls with COVID-19 4. To compare the COVID-19 severity in PLWHIV and controls at diagnosis and hospital admission.
Outcome Measures	**Primary** 1. The primary endpoint is a composite of: Critical care admission (high dependency unit or intensive care unit), mortality in hospital or palliative discharge when discharged from hospital, or mortality at 6 weeks after diagnosis of COVID-19 or at discharge from hospital (where applicable)	**Secondary** 1. Hospitalisation for COVID-19 2. Length of stay in hospital 3. Length of stay on ICU 4. Number of ventilator-free days (VFDs) 5. Length of extracorporeal membrane oxygenation (ECMO) 6. Need for kidney replacement therapy 7. Measurement of total comorbidity burden using the Charlson Comorbidity Index (CCI) and age-adjusted CCI (ACCI) 8. Estimate risk of 30-day mortality after COVID-19 infection using pre-COVID health status (estimated using the Veterans Health Administration COVID-19 (VACO) index) 9. Inflammatory marker and blood cell counts at COVID-19 diagnosis

FUNDING AND SUPPORT

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LIST OF ABBREVIATIONS

Acronym	Description
ACCI	Age-adjusted Charlson Comorbidity Index
ART	Antiretroviral Therapy/Treatment
ARV	Antiretroviral
CCI	Charlson Comorbidity Index
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
EC	European Commission
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
GDPR	General Data Protection Regulation
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practice
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ISF	Investigator Site File
ISPE	International Society for Pharmacoepidemiology
MS	Member State
R&D	Research & Development
PI	Principal Investigator
PLWHIV	People Living With HIV
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMF	Trial Master File
VACO	Veterans Health Administration COVID-19
VFD(s)	Ventilator-Free Day(s)

1. BACKGROUND

COVID-19 is a public health emergency of international concern with mortality rates of 2-4% and highest death risk in elderly male patients and those with co-morbidities. Little is known about the disease course of COVID-19 in specific patient groups with immunosuppression or people living with HIV (PLWHIV) [1-5] and whether PLWHIV may have some degree of protection due to their ART compounds [6-9]. Irrespective of their antiretroviral therapy, PLWHIV with co-morbidities are expected to accumulate risk factors for COVID-19. Also, incomplete immune reconstitution may put them at risk for severe COVID-19.

2. RATIONALE

Current evidence indicates that the risk of severe COVID-19 illness increases with age, male gender and with certain chronic medical problems such as arterial hypertension, cardiovascular disease, chronic lung disease, obesity and diabetes. Whether or not PLWHIV on treatment with a normal CD4 cell count and suppressed HIV-RNA are at an increased risk of serious illness or death, many will have other conditions that increase their risk. Indeed, almost half PLWH in Europe are older than 50 years and chronic medical conditions, including cardiovascular and chronic lung disease, are more common in PLWHIV.

Case series of PLWHIV with COVID-19 from China, Spain, Germany, Italy and the United States [10-22] show no clear evidence for a higher COVID-19 infection rate or different disease course in people with and without HIV. Of note, most case series of PLWHIV report a younger age in their study population than in HIV-negative hospitalised COVID-19 patients, but comparable rates of comorbidities. A cohort study from the United Kingdom reported a small potential increase in the risk of mortality among PLWHIV once hospitalised with COVID-19, albeit with no data around the risk of developing severe COVID-19 or hospitalisation among this cohort in the first place and no data on antiretroviral therapy (ART), viral load (VL) or CD4 count [23].

An analysis of risk factors for COVID-19 deaths in the Western Cape [24] described after adjusting for other risk factors that HIV increased a COVID-19 patient's death risk by a factor of 2.14 (95% CI 1.70;2.70), and active TB by a factor of 2.70 (95% CI 1.91-4.04). Finally, Spanish researchers described the incidence of COVID-19 and risk of hospitalization among 77,590 PLWHIV receiving ART [7]. During a 3-month period, 236 PLWHIV were diagnosed with COVID-19, and 151 were hospitalized. The risk of hospitalization by NRTI treatment per 10,000 persons was lowest for TDF/FTC (10.5), while other NRTI strategies were similar.

Data regarding the activity of TDF against SARS CoV-2 is conflicting. In Silico data suggests that TDF/FTC may bind to SARS CoV-2 Nsp1 protein [25], an unreviewed study shows that TDF and TAF may inhibit the SARS-CoV-2 polymerase [26], one in vitro study supports antiviral activity of TDF/FTC [27] and an animal models suggest shortened duration of symptoms, and possibly infectiousness [28]. However, two studies have failed to demonstrate any in vitro activity of tenofovir against CoV-2 [29,30]. There is ongoing discussion and research around other antiretrovirals, which may have some activity against COVID-19. The first randomised clinical trial (RCT) with lopinavir-ritonavir (LPV/r) demonstrated no benefit over standard care in 199 hospitalised adults with severe COVID-19 [31]. Since then the large UK RECOVERY trial, which to date has randomised almost 12,000 people hospitalised with COVID-19 to different therapeutic options, has stopped recruitment to the LPV/r arm after a review by Data Monitoring Committee revealed no benefit of LPV/r over standard of care in terms of mortality, ventilation requirement or length of stay [32]. Moreover, an Italian case series suggests boosted DRV

does not prevent SARS-CoV-2 infection in PLWHIV or protect against worsening respiratory function [33].

Rapid data collection and analysis about COVID-19 in PLWHIV will depend on international multi-centre collaborations, for which NEAT ID has a strong expertise. The majority of PLWHIV in Europe are in routine clinical care, allowing for a comprehensive data collection about COVID-19 and studying the impact of HIV drugs and specific risk factors. The NEAT ID COVID-19 Coinfection Dashboard was established in March 2020 to collect data on the number of PLWHIV co-infected with COVID-19 in Europe and has provided evidence that a significant number of PLWHIV are suffering from COVID-19 in Europe already and that these individuals can be enrolled into an Epidemiology and Real-World-Data study.

There are two central questions to address:

1. Is there a particular risk for COVID-19 in PLWHIV as compared to HIV seronegative control COVID-19 cases?

2. Are there particular factors, within the group of PLWHIV, which put them at risk for a more severe COVID-19 disease course?

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

It is hypothesised that HIV infection is a risk factor for more severe COVID-19 outcomes and that advanced immunodeficiency as defined by current CD4 T-cell count or CD4 T-cell nadir is a risk factor for more severe COVID-19 outcomes in PLWHIV.

3.1 Primary objective

1. To describe outcomes of COVID-19 in PLWHIV in comparison to HIV seronegative COVID-19 controls.
2. To identify risk factors (e.g. CD4 cell nadir, current CD4 count, co-morbidities) for severe COVID-19 outcomes within the group of PLWHIV.

3.2 Secondary objectives

1. To describe differences in the clinical manifestation of COVID-19 in PLWHIV as compared to HIV seronegative controls.
2. Describe, where appropriate, the response to treatment, including supportive care and novel therapeutics against COVID-19, including antiviral and immunomodulatory therapies
3. To describe the co-morbidities in PLWHIV and controls with COVID-19
4. To compare the COVID-19 severity in PLWHIV and controls at diagnosis and hospital admission.

3.3 Primary endpoint/outcome

1. The primary endpoint is a composite of: Critical care admission (high dependency unit or intensive care unit), mortality in hospital or palliative discharge when discharged from hospital, or mortality at 6 weeks after diagnosis of COVID-19 or at discharge from hospital (where applicable)

3.4 Secondary endpoints/outcomes

1. Hospitalisation for COVID-19
2. Length of stay in hospital
3. Length of stay on ICU
4. Number of ventilator-free days (VFDs)
5. Length of extracorporeal membrane oxygenation (ECMO)
6. Need for kidney replacement therapy
7. Measurement of total comorbidity burden using the Charlson Comorbidity Index (CCI) and age-adjusted CCI (ACCI)
8. Estimate risk of 30-day mortality after COVID-19 infection using pre-COVID health status (estimated using the Veterans Health Administration COVID-19 (VACO) index)
9. Inflammatory marker and blood cell counts at COVID-19 diagnosis

4 STUDY DESIGN

This is an observational, retrospective, case-control study.

4.1 Study Schema

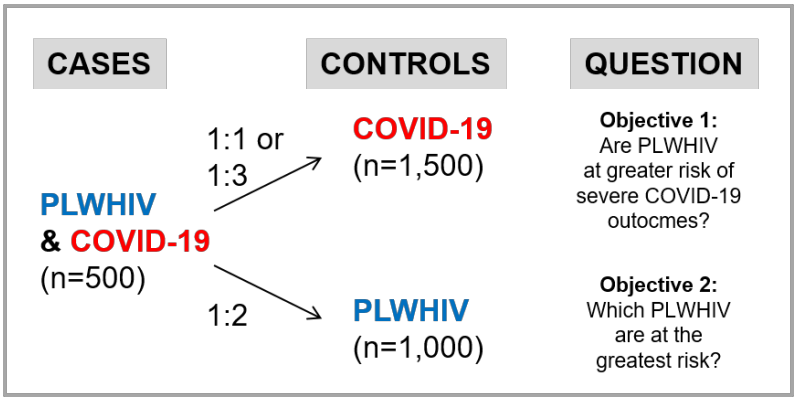

Figure 1: Study design with cases (PLWHIV & COVID-19) and two matched control groups.

In total, 500 cases and up to 2500 controls will be analysed.

Only real-world retrospective data will be used for this study. Deidentified retrospective data will be transcribed into the eCRF system from source data at each clinical site or from existing COVID-19 cohort databases, where appropriate.

For comparing PLWHIV & COVID-19 versus HIV seronegative COVID-19 patients, a 1:1 and 1:3 matching will be performed according to the following criteria:

- Age (+/- 5 years)
- Sex
- Ethnicity (where available)
- Month of COVID-19 diagnosis (+/- 2 months)
- COVID-19 diagnosis inpatient, 1:1 matching
  OR
- COVID-19 diagnosis outpatient (ambulatory), 1:3 matching

For comparing PLWHIV & COVID-19 versus PLWHIV without COVID-19, a 1:2 matching for similar risk of acquiring COVID-19 will be performed according to the following criteria:

- Age (+/- 5 years)
- Sex
- Ethnicity (where available)

5 ELIGIBILITY CRITERIA

The study population will consist of adult PLWHIV with and without COVID-19 disease and followed up at the study sites for routine clinical care. In addition, data from adult COVID-19 patients without HIV infection will be used as controls.

Cases (PLWHIV + COVID-19) will be at least 18 years of age with documented HIV-1 infection and confirmed SARS-CoV-2 infection by documented, or patient-reported, positive result on PCR testing of a nasopharyngeal or respiratory sample, before 1st April 2021.

Controls (COVID-19) will be at least 18 years of age without documented HIV-1 infection but confirmed SARS-CoV-2 infection by documented, or patient-reported, positive result on PCR testing of a nasopharyngeal or respiratory sample, before 1st April 2021.

The second control group (PLWHIV) will include individuals at least 18 years of age with documented HIV-1 infection.

5.1 Inclusion Criteria

- Cases (PLWHIV + COVID-19)
    - Any gender
    - At least 18 years of age
    - Documented HIV-1 infection
    - Confirmed SARS-CoV-2 infection by documented, or patient-reported, positive result on PCR testing of a nasopharyngeal or respiratory sample, before 1st April 2021

Each case should be matched to a control (1:1 or 1:3 respectively for COVID-19 controls and 1:2 for PLWHIV controls) according to the matching criteria set out in section 4.1.

- Controls (COVID-19)
    - Any gender
    - At least 18 years of age
    - No documented HIV-1 infection
    - Confirmed SARS-CoV-2 infection by documented, or patient-reported, positive result on PCR testing of a nasopharyngeal or respiratory sample, before 1st April 2021
    - Meet the matching criteria
- Controls (PLWHIV)
    - Any gender
    - At least 18 years of age

- Documented HIV-1 infection
- No evidence of SARS-CoV-2 infection
- Meet the matching criteria

5.2 Exclusion Criteria

- COVID-19 diagnosed based on clinical criteria

6 STUDY PROCEDURES

6.1 Subject Identification

Most PLWHIV will be identified from sites in the NEAT ID network. PLWHIV are routinely followed-up at specialised outpatient clinics with regular follow up visits as standard of care.

Since March 2020, more than 50 European sites have registered and started to provide basic information about the number of PLWHIV with COVID-19 and disease outcomes at their centres (https://www.NEAT-ID.org/). The dashboard provides a first estimate about the total numbers of PLWHIV with COVID-19 and where these patients are in continued care. As of 26th April 2021, 1,187 PLWHIV with COVID-19 were reported in care across Europe, with 436 hospitalisations and 78 deaths from an estimated number of 85,279 PLWHIV in routine care at these sites. These case numbers strongly suggest feasibility to recruit sufficient numbers of PLWHIV with COVID-19 and that patients have been identified at their centres already.

6.2 Data collection

Only real-world retrospective data will be used for this study. Deidentified retrospective data will be transcribed into the eCRF system from source data at each clinical site or from existing COVID-19 cohort databases, where appropriate. No personal identifiable data will be transmitted to NEAT ID. The data elements will be transcribed from source data according to the data collection list below. Mechanisms to ensure data quality and integrity will be deployed as per applicable standard operating procedures and in line with GCP and GPP. Patients and controls will be identified and documented by participating sites, provided unbiased matching for inpatient/outpatient status at the time of COVID-19 diagnosis is ensured. Alternatively, and to avoid potential site-related bias during selection of HIV negative controls with COVID-19 diagnosed in hospital, data from matched controls will be obtained from appropriate existing COVID-19 cohort databases, e.g. LEOSS (Lean European Open Survey on SARS-CoV‑2 infected patients) or ISARIC (International Severe Acute Respiratory and emerging Infection Consortium).

For all patients the following information will be collected:

- Age
- Sex
- Ethnicity (where available)
- Comorbidities (see appendix 1)
- Weight (kg) and height (m) (to calculate BMI)

For patients with COVID-19 the following information will be collected (where applicable):

- Date of positive PCR test result (documented or patient-reported)
- COVID-19 diagnosis inpatient or outpatient
- All-cause mortality in hospital, or palliative discharge, or mortality at 6 weeks after diagnosis of COVID-19 or at discharge from hospital
- Hospitalisation for COVID-19 and length of hospitalisation
- Critical care admission (high dependency unit or intensive care unit) for COVID-19 and length of stay in critical care
- Length of invasive ventilation
- Length of extracorporeal membrane oxygenation (ECMO)
- Need for kidney replacement therapy
- Inflammatory markers and blood cell counts at COVID-19 diagnosis[1] (if available):
    - Full blood cell count (Platelet count, RBC Count, WBC count (absolute), Haemoglobin, Haematocrit, MCV, MCH, Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils), ALT, AST, total bilirubin, urea, serum creatinine, calcium, glucose and HbA1C levels, total cholesterol, triglycerides, CRP, D-dimer, ferritin, and lactate dehyrodgenase
- Drug treatment for COVID-19 (glucocorticoids, azithromycin, remdesivir, monoclonal antibodies against SARS-CoV2, reconvalescent plasma, anti-IL1 inhibitors, anti-IL6 inhibitors, lopinavir/ritonavir, and others)

For PLWHIV the following information will be collected:

- Date of HIV diagnosis
- Current ART
- CDC disease stage
- CD4 cell nadir
- Last CD4 cell count (including CD4% and CD4/CD8 ratio) and HIV-RNA before COVID-19 diagnosis, or most recent for HIV-only controls

7 STATISTICS AND DATA ANALYSIS

7.1 Sample size calculation

The US Veterans Ageing Cohort Study (VACS) reported at AIDS 2020 [20] that the estimated proportion of non-HIV-infected individuals hospitalized with COVID-19 was 35%, 15% in ICU, 8% with invasive mechanical ventilation and 11% died. We anticipate a 1.1 to 2-fold increase in hazard rate in PLWHIV & COVID-19 (cases) relative to HIV-negative & COVID-19 (controls). With 500 cases and 1500 controls, a two-sided log-rank test at an alpha level of 0.05 will achieve at least 80% power to detect a 1.3-fold increase in the hazard rate of hospitalization, 1.4 for ICU, 1.6 for invasive mechanical ventilation and 1.5 for death (refer to Table 1 below). The power calculation was made using the statistical software package nQuery Advanced, with the two samples Log-Rank test module (Version 8.6.1.0).

Table 1

[1] Most recent available after positive SARS-CoV-2 PCR test, up to 10 days after positive test

		Cases (PLWHIV & COVID-19, N=500); Controls (HIV-negative & COVID-19, N=up to 1500) Alpha=5% (two-sided)									
Severity outcome	Outcome (%)	**Power (%)**									
Hazard Risk		**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**	**1.9**	**2.0**
Hospitalization	35	20	60	90	99	>99	>99	>99	>99	>99	>99
ICU	15	11	31	58	81	94	99	>99	>99	>99	>99
Invasive mechanical ventilation	8	8	19	35	54	73	86	94	98	99	>99
Death	11	9	24	46	68	85	95	98	>99	>99	>99

For the search for factors associated with SARS-CoV-2 infection in PLWHIV, the recommended rule of thumb for sample size estimation for multivariable logistic regression models was n = 100 + 50i where i refers to number of independent variables in the final model [34]. With 1500 PLWHIV (500 with COVID-19 and 1500 controls without COVID-19), we would be able to study 28 parameters with sufficient power to produce statistics that are nearly representative of the true values in the targeted population. However, sample size less than 1500 may be sufficient for associations that yield medium to large effect size.

7.2 Planned recruitment rate

We believe that approximately 30 European sites could participate. Therefore, we estimate that about 60-80 patients would need to be recruited per site to reach the total number of subjects required.

7.3 Statistical analysis plan

The statistical hypotheses are: 1) to show whether HIV infection is associated with severe COVID-19 compared to HIV uninfected individuals; 2) and to identify factors associated with severe COVID-19 within HIV infected population. All eligible subjects with a matching individual will be included in the analysis population (full population analysis).

Time-to-event methods, including Kaplan–Meier survival curves and Cox proportional-hazards models, will be used to compare PLWHIV with COVID-19 versus HIV seronegative COVID-19 controls for the severity of COVID-19 using parameters collected and adjusted for potential confounders. Conditional logistic regression models will be used to assess factors associated with COVID-19 within the group of PLWHIV to account for the case-control matching.

7.3.1 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.

7.3.2 Primary outcome analysis

The first primary outcome analysis will be performed on PLWHIV with COVID-19 versus HIV uninfected individuals with COVID-19. The endpoint is the occurrence of critical care admission (high dependency unit or intensive care unit), mortality in hospital or palliative discharge when discharged from hospital, or mortality at 6 weeks after diagnosis of COVID-19 or at discharge from hospital (where applicable). Kaplan-Meier estimates will be used to estimate the proportion of participants with the primary endpoint events. Unadjusted and adjusted hazard ratios (HR) will be estimated using the Cox proportional hazard model to assess the impact of HIV-infection on the severity of COVID-19. The validity of the proportionality assumption will be assessed and tested. The adjusted variables will be the following (potential confounders): Age (<60 vs 60-64 vs 65-69 vs 70-74 vs ≥75 years); Sex at birth (female vs male); Obesity (BMI>30 kg/m^2); and Comorbidities (see appendix 1).

The second primary outcome analysis will be performed within the group of PLWHIV (PLWHIV with COVID-19 versus PLWHIV without COVID-19). The endpoint is to assess factors associated with severe COVID-19 within the group of PLWHIV. Conditional logistic regression models will be used to account for the case-control matching. The following variables will be assessed: Age (<60 vs 60-64 vs 65-69 vs 70-74 vs ≥75 years); Sex at birth (female vs male); Obesity (BMI >30 kg/m^2); Comorbidities (see appendix 1); time since HIV diagnosis (years); current ART; CDC disease stage; CD4 cell nadir; last CD4 cell count/HIV-RNA before COVID-19 diagnosis (including CD4% and CD4/CD8 ratio) at baseline. For continuous variables, the decision to treat the variable as a continuous or categorical variable (as tertile) will be based on the lowest Akaike information criterion value for the corresponding univariable conditional logistic regression analysis. Variables achieving $P < 0.20$ in the univariable analysis will be retained for the multivariable analysis.

7.3.3 Secondary outcome analysis

All secondary outcome analysis will be performed on PLWHIV with COVID-19 compared to HIV uninfected individuals with COVID-19.

The proportion of hospitalised patients for COVID-19, the length of stay in hospital, the length of stay on ICU, the length of extracorporeal membrane oxygenation (ECMO), and the proportion of participants with a need for kidney replacement therapy will be estimated using the Kaplan-Meier estimate. Unadjusted and adjusted hazard ratios (HR) will be estimated using the Cox proportional hazard model to assess the impact of HIV-infection on the severity of COVID-19. The adjusted variables will be the same as those used for the first primary outcome analysis.

The number of ventilator-free days (VFDs) will be compared between groups using competing risk regression, with extubation and mortality a competing event, adjusted for potential confounders.

Linear regression models will be used to compare Charlson Comorbidity Index (CCI), the age-adjusted CCI (ACCI), 30-day mortality index after COVID infection, inflammatory marker and blood cell counts at COVID-19 diagnosis between the 2 groups, adjusted for potential confounders. The sample size will be quite large to consider CCI, 30-day mortality index, inflammatory marker and blood cell counts as normally distributed variables.

7.4 Subject population

All eligible subjects with a matching individual will be included in the analysis population (full population analysis).

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

Multiple imputation using Chained Equations approach (MICE) will be used to fill in missing data. Ten imputations (M=10) will be chosen to obtain valid inference and reduce sampling variability resulting from the imputation process. Variables with a missing rate above 15% will be excluded and the outcomes will be included in the imputation model. All 10 datasets will be analyzed and combined using Rubin rules.

8 DATA HANDLING

8.1 Dissemination of results, authorship eligibility guidelines and any intended use of professional writers

Data from the study will be published independently by NEAT ID. All contributing PI investigators will have the opportunity to participate in publication (abstracts and manuscripts) on the analyses.

This study will be reported in line with the STROBE Statement for reporting observational studies. Details of this study and the results will be available on a freely accessible clinical trial registry (ISRCTN, clinicaltrials.gov or equivalent) and will be presented/disseminated at appropriate conferences.

8.2 Data Protection

Personal Data means any information relating to an identified or identifiable natural person (Data Participant), including without limitation pseudonymised information, as defined in the Applicable Law. The *Applicable Law* includes the Regulation (EU) 2016/679, its UK counterpart (UK GDPR) and other relevant regulations. Personal Data will only be collected in line with the study objectives as descried in this protocol, and to safeguard participants' rights, only relevant, adequate, limited and necessary data will be collected and used. It is the Data Controller's (the sponsor) responsibility to ensure compliance with the Applicable Law of a data processor (a CRO or an investigator site).

Data processor(s) to aid the Controller with the Applicable Law compliance, must ensure that persons authorised to process the data, have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality. Transfer of data must be strictly necessary for the implementation of the research or the use of the results. Transfers of data to a third country will be carried out in line with the applicable law and/or provisions ensuring adequacy (e.g. Standard Contractual Clauses for the transfer of personal data).

Data participant rights are upheld according to the applicable law. If a consent has been given, that consent may be withdrawn at any time. The withdrawal will not affect the lawfulness of the processing carried out prior. The personal data may continue to be processed where there is an appropriate legal basis for such processing. Rights to access, change or move of the collected information are limited as

the information must be managed in specific ways for the research to be reliable and accurate.

8.3 Data Retention

Patient data may be retained for up to two (2) years after the last publication of the results of research or, in the absence of publication, until the signing of the final research report.

The personal data of professionals involved in research cannot be kept beyond a period of fifteen years (or in accordance with the current regulations) after the end of the last research in which they participated.

9 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Research Ethics Committee (REC) review & reports

- Before the start of the trial, approval will be sought from a REC and/or any other applicable bodies for the trial protocol and other relevant documents
- Where applicable a notification will be submitted to a Competent Authority in accordance with the country regulations
- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the Competent Authority and/or local R&D departments before they can be implemented in practice at sites)
- All correspondence with respect to submissions and approvals will be retained in the Trial Master File/Investigator Site File
- An annual progress report (APR) will be submitted to the REC(s) within 30 days of the end of the reporting period, and annually until the trial is declared ended
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC(s) of the end of the study
- If the study is ended prematurely, the Chief Investigator will notify the REC(s), including the reasons for the premature termination
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC(s)

9.2 Peer review

This protocol has undergone peer review as per NEAT ID's standard peer review process.

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11 APPENDICIES

APPENDIX 1 – Comorbidity Variables & Definitions

VARIABLE	DEFINITION
Myocardial Infarction (heart attack)	History of definite or probable MI (EKG changes and/or enzyme changes)
Congestive Heart Failure	Exertional or paroxysmal nocturnal dyspnoea and has responded to digitalis, diuretics, or afterload reducing agents
Peripheral Vascular Disease	Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6 cm)
Cerebrovascular Accident (stroke) or Transient Ischemic Attack	History of a cerebrovascular accident with minor or no residua and transient ischemic attacks
Dementia	Chronic cognitive deficit
Chronic Obstructive Pulmonary Disease	-
History of Pneumonia	-
Connective Tissue Disease • **Rheumatologic Disease** • **Any Other**	-
Peptic Ulcer Disease	Any history of treatment for peptic ulcer disease or history of peptic ulcer bleeding
Liver Disease • **Mild** • **Moderate** • **Severe**	Mild = chronic hepatitis (or cirrhosis without portal hypertension) Moderate = cirrhosis and portal hypertension but no variceal bleeding history Severe = cirrhosis and portal hypertension with variceal bleeding history
Diabetes • **None or Diet-Controlled** • **Uncomplicated** • **With Complications**	-
Hemiplegia	-
Paralysis of Arm(s) or Leg(s)	-
Chronic Kidney Disease • **Moderate**	Moderate = creatinine >3 mg/dL (0.27 mmol/L) Severe = on dialysis, status post kidney transplant, uraemia

• **Severe**	
Current or History of Cancer • **Localised** • **Metastatic**	-
Leukaemia	-
Lymphoma	-
AIDS	-

APPENDIX 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1.0	28June2021	Prof Georg Behrens, CI Jacob Lowman, Clinical Project Manager	Initial version
01	2.0	10NOV2021	Prof Georg Behrens, CI Jacob Lowman, Clinical Project Manager	Addition of inclusion criteria for COVID-19 diagnosis confirmed before 1st April 2021 only. Addition of matching criteria for COVID-19 diagnosis inpatient or outpatient. Addition of wording to allow for flexibility in use of existing COVID-19 cohort databases.
02	Draft 2.1	29AUG2022	Prof Georg Behrens, CI Kathryn Fellows, Clinical Project Manager	Addition of COVID-19 only controls to be increased up to 1500 Addition of wording to allow for 1:3 matching on COVID-19 only data.

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