PROTOCOL

CLINICAL TRIAL PROTOCOL

Simplified model of access and retention to the healthcare system, using a mobile unit and a same-day diagnosis and treatment strategy in vulnerable populations. SIMPLIFIED Study.

Drug: BIC/FTC/TAF

Protocol version and date: V 4.0 of July 21, 2023

Study name: SIMPLIFIED

Sponsor: Fundación SEIMC-GESIDA

Protocol code: GeSIDA 122-21

EudraCT: 2021-005546-15

CONFIDENTIAL

PROTOCOL SIGNATURE PAGE

Protocol Code:

The information contained in this document and all information provided to you in relation to this interventional study is confidential and property of the sponsor, and except as required by local or state laws and regulations, it must not be disclosed without prior written consent from the sponsor. The principal investigator may, however, disclose such information to the personnel under their charge working on the study, provided that such personnel agree to maintain confidentiality regarding said information.

- I have read and understood the protocol, including the appendices.

- I agree to conduct the interventional study in accordance with the investigator's obligations contained in the protocol and the recommendations of the International Conference on Harmonisation Tripartite on Good Clinical Practice (in force in Europe since January 17, 1997).

- All changes in procedures will be made, if necessary, only to protect the safety, rights or welfare of the patients.
- I agree to respect the confidentiality commitment.

PABLO RYAN MURUA Date:..... Signature:..... Coordinating Investigator

JORGE VALENCIA DE LA ROSA Date:..... Signature:..... Coordinating Investigator

ABBREVIATIONS

AEMPS	Spanish Agency for Medicines and Health Products
ALT	Alanine aminotransferase
RNA (ARN)	Ribonucleic acid
AST	Aspartate aminotransferase
BIC	Bictegravir
CDC	Centers for Disease Control
ERC (CEI)	Ethics Research Committee
mERC (CEIm)	Ethics Committee for Research with medicines
IC (CI)	Informed consent
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COBI	Cobicistat
e-CRF (CRD-e)	Electronic Case Report Form
DAIDS	Division of AIDS
DBS	Dried blood sample
AE (AA)	Adverse Event
SAE (AAG)	Serious Adverse Event
ALP (FA)	Alkaline phosphatase
FDA	U.S. Food and Drug Administration
FTC	Emtricitabine
VF (FV)	Virological failure
GESIDA	Spanish AIDS Study Group
GGP2	Good Publication Practice 2
HIV-TSQ	Patient treatment satisfaction questionnaire
CI (IC)	Confidence Interval

AEMPS	Spanish Agency for Medicines and Health Products
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
PI (InP)	Protease inhibitor
INR	International normalized ratio
INSTI	Integrase strand transfer inhibitor
PI (IP)	Principal investigator
NRTI (ITIAN)	Nucleoside reverse transcriptase inhibitor
NNRTI (ITINAN)	Non-nucleoside reverse transcriptase inhibitor
ITT	Intention to treat
LDH	Lactate-dehydrogenase
LLOD	Lower limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliters
DBP (PAD)	Diastolic blood pressure
SBP (PAS)	Systolic blood pressure
PP	Per protocol
PREM	Patients reported experiences measures
PROM	Patients reported outcome measures
VP (PV)	Vulnerable populations
QD	Once daily
SUSAR (RAGI)	Suspected Unexpected Serious Adverse Reaction
AIDS (SIDA)	Acquired immunodeficiency syndrome
SMADS	Mobile Service
SMAQ	Adherence scale

AEMPS	Spanish Agency for Medicines and Health Products
STR	Single tablet regimen
TAF	Tenofovir alafenamide
ART (TARV)	Antiretroviral therapy
GFR (TFG)	Glomerular filtration rate
RT (TI)	Reverse transcriptase
PT (TP)	Prothrombin time
EU (UE)	European Union
MSU (UMC)	Mobile Screening Unit
HBV (VHB)	Hepatitis B Virus
HCV (VHC)	Hepatitis C Virus
HIV (VIH)	Human immunodeficiency virus

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1. Summary

SPONSOR DATA	Fundación SEIMC-GESIDACalle Agustín de Betancourt, 13 – entreplanta, Madrid, 28003. Spain.
PROTOCOL CODE	GeSIDA 122-21
PROTOCOL VERSION AND DATE	Version and date: 3, April 5, 2022
STUDY TITLE IN SPANISH	Modelo simplificado de acceso y retención al sistema sanitario, utilizando una unidad móvil y una estrategia de diagnóstico y tratamiento en el mismo día en poblaciones vulnerables. Estudio SIMPLIFIED.
STUDY TITLE IN ENGLISH	Simplified model of linkage & retention to care, using a mobile unit and a same-day test & treat approach among excluded population. The SIMPLIFIED Study.
CLINICAL TRIAL PHASE	Phase IV clinical trial
IDENTIFICATION OF INVESTIGATORS	**Coordinating Investigator:** Dr. PABLO RYAN MURUA Hospital Universitario Infanta Leonor C/Gran Via del Este 80, 28031 Madrid Telephone: +34 616832148 E-mail: pabloryan@gmail.com Dr. JORGE VALENCIA LA ROSA FUNDACION de INVESTIGACION Hospital Universitario Infanta Leonor y Hospital Universitario Sur Este C/Gran Via del Este 80, 28031 Madrid E-mail: jorge_vlr@yahoo.es
STUDY OBJECTIVES	**Objectives** **Primary Objective** To determine if the implementation of a HIV care access and retention model for vulnerable people using a mobile screening unit and a same-day diagnosis and treatment initiation strategy is effective and safe.

SPONSOR DATA	Fundación SEIMC-GESIDACalle Agustín de Betancourt, 13 – entreplanta, Madrid, 28003. Spain.
	Secondary Objectives To evaluate the implementation and feasibility of the intervention.
STUDY POPULATION	1. Participants wishing to participate in the study must meet all the criteria listed below: 2. Vulnerable person ≥18 years old. 3. Understand and sign the informed consent. 4. Confirmed HIV infection. 5. Not receiving ART or being on ART with plasma viral load (PVL) >1000 copies/ml. **Exclusion Criteria** Participants presenting any of the following criteria may not participate: 1. Inability to provide contact data. 2. History of allergy to any of the following drugs: bictegravir, tenofovir alafenamide, or emtricitabine. 3. Taking antiretroviral treatment for less than 1 month. 4. Pregnancy or breastfeeding at the time of screening or gestational desires during the study period. 5. Suspicion or diagnosis of active opportunistic disease. 6. History of severe liver disease (Child-Pugh C) or history of decompensated liver disease (defined as the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice).

SPONSOR DATA	Fundación SEIMC-GESIDACalle Agustín de Betancourt, 13 – entreplanta, Madrid, 28003. Spain.
	7. History of renal disease CKD-EPI <30ml/min. 8. Presenting any condition that, in the investigator's opinion, makes the patient not a candidate for inclusion (Active disease, social situation, intoxication…).
NUMBER OF PARTICIPANTS	100 participants
INVESTIGATIONAL PRODUCT, DOSAGE AND ROUTE OF ADMINISTRATION	Participants will receive a single oral dose of BIC/FTC/TAF (three drugs formulated in one pill) every day for 12 months. • Bictegravir (BIC) 50 mg • Emtricitabine (FTC) 200 mg • Tenofovir alafenamide (TAF) 25 mg
ASSESSMENT OF TRIAL ENDPOINTS	**1.1. Evaluate the effectiveness of the strategy** • Proportion of subjects who agree to participate in the study. • Proportion of subjects who start ART after inclusion. • Median time from study inclusion to the start of ART. • Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at 24 weeks after inclusion. • Absolute values and changes from baseline in CD4+ cell count and CD4:CD8 ratio at 24 weeks. • Proportion of subjects who attend visits at weeks 24 and 48.

SPONSOR DATA	Fundación SEIMC-GESIDACalle Agustín de Betancourt, 13 – entreplanta, Madrid, 28003. Spain.
	1.2. Evaluate the safety of the strategy • Incidence and severity of adverse events (clinical and laboratory) up to week 24. • Incidence of adverse events leading to treatment discontinuation up to week 24. • Incidence of genotypic resistance mutations in participants with virological failure at week 48. **1.3. Evaluate the implementation of the strategy** • Evaluation of the acceptability, comfort, suitability, usefulness, adequacy, quality and perceived benefit and satisfaction of the intervention (Appendix 6) at the baseline visit and at the week 24 visit. These parameters will be collected using a scale from 0 to 5. • To evaluate the implementation of this project, in addition to the aspects in the previous point, the endpoints referred to above (Evaluate the effectiveness of the strategy and Evaluate the safety of the strategy) will be used.
STATISTICS	Efficacy, safety, and intervention perception analyses will be performed using the intention-to-treat population. Aspects relating to the use of the service or intervention will be performed using the included population.
STUDY DURATION	The study duration is defined for each participant as the date on which the signed written informed consent is provided until the last follow-up visit, which may be up to week 48.
ETHICS COMMITTEE EVALUATOR	The study will be evaluated by the Ethics Committee for Research with medicines (CEIm) of H. Severo

SPONSOR DATA	Fundación SEIMC-GESIDACalle Agustín de Betancourt, 13 – entreplanta, Madrid, 28003. Spain.
	Ochoa, accredited by the Ministry of Health and by the health authorities of the Community of Madrid.

2. Flowchart

Phase	Screening	Treatment	Early Withdrawal
Visit		V 1	V 2
Weeks (± days window period)	(-10)	0	4 (±5)
Informed Consent	X		
Medical History	X		
Drug Consumption Registry	X		X
Inclusion/Exclusion (a)	X		
Complete Physical Examination (b)		X	
Resistance Study (c)			X
Pregnancy Test (d)	X	X	X
Complete Blood Count (e)		X	X
Biochemistry (e)		X	X
Phase	**Screening**	**Treatment**	**Early Withdrawal**
Visit		**V 1**	**V 2**
Weeks (± days window period)	**(-10)**	**0**	**4 (±5)**
Serologies (e)		X	
Immunology and Virology (e)		X	X
Hepatitis C Rapid Test (e, f)	X		X
Questionnaires (g)	X		
Concomitant Medication Review	X	X	X
BIC/FTC/TAF Dosing (h)		X	X
ART Adherence (i)			X
Review Adverse Effects (j)		X	X
Social Situation (k)	X		X

Abbreviations: Wk, week; V, visit.

Notes:

- a) The screening visit and Visit 1 (treatment initiation) may be performed on the same day.
- b) See Physical Examination section.
- c) In case of virological failure, a resistance study will be performed.
- d) Urine pregnancy test; in case of a positive result, confirm with a blood sample.
- e) These procedures will be performed at the center's laboratory. See Clinical Laboratory Analysis section.
- f) In the case of a previous negative serology or rapid test.
- g) Questionnaires on the perception and experience of program participation. Collected via a paper form by the investigator. These must be kept in the investigator's file (see Appendix 5 and 6).
- h) BIC/FTC/TAF dosing will be administered orally once daily.
- i) SMAQ Adherence Questionnaire (Appendix 7) and pill count.
- j) Adverse effects. They require monitoring.
- k) Social situation of the participant. Daily activity, employment status, housing and overnight stay location.
- l) Via telephone call.

3. Introduction

The HIV epidemic is far from being eradicated. According to 2020 WHO and UNAIDS data, there are 37.7 million infected people in the world, 1.5 million of which are new diagnoses (1). In Spain, the overall rate of new HIV diagnoses is currently at levels similar to those of other countries in the WHO European Region. However, although the improvement compared to past decades is undeniable, the rate is higher than the average for the European Union and Western European countries. As of June 30, 2020, notifications of 2,698 new HIV diagnoses in 2019 were received from 15 Autonomous Communities and Ceuta, representing a rate of 5.94 per 100,000 inhabitants without adjusting for reporting delay. Transmission in men who have sex with men (MSM) was the most frequent, at 56.6%, followed by heterosexual transmission, which accounted for 32.3%, and transmission occurring in people who inject drugs (PWID), which totaled 2.6% (2).

The transmissibility of HIV is linked to the plasma viral load (PVL); and PVL below 1,000 copies/mL of HIV-RNA has a significantly lower risk of transmission (3). Based on this, a goal for the year 2020 called 90-90-90 was proposed: an ambitious treatment target to help end the AIDS epidemic (by 2020, 90% of all people living with HIV will know their HIV status; 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy, and 90% of all people receiving antiretroviral therapy will have viral suppression (4). However, in 2020, of all people living with HIV, 84% [67-98%] knew their serological status, 73% [56-88%] accessed treatment, and 66% [53-79%] had viral suppression.

In 2020, key populations (sex workers and their clients, gay men and other men who have sex with men, people who inject drugs, transgender people) and their sexual partners accounted for 65% of HIV infections worldwide. The risk of contracting HIV is 35 times higher among people who inject drugs, 26 times higher among sex workers, and 25 times higher among men who have sex with men (MSM).

Early initiation of antiretroviral therapy (ART) reduces the morbidity and mortality of HIV-infected individuals (5). Suppression of viral replication with ART also reduces the potential for HIV transmission (6). Therefore, antiretroviral treatment is recommended for all individuals with HIV viremia, regardless of the CD4 lymphocyte count. Modern ART regimens are now more potent and relatively simple to administer. Several studies have shown that a decrease in pill burden and dosing frequency is associated with increased adherence and that early initiation of ART is associated with better immunovirological recovery.

With classic antiretrovirals, the HIV epidemic continues to grow and new therapies began, such as "pre-exposure prophylaxis" (the use of antiretroviral drugs as a way to prevent new infections among people at highest risk) with Tenofovir Disoproxil Fumarate (TDF), but clinical trials have had highly variable results depending on the level of adherence (7). Another strategy was the rapid initiation of ART for those who tested positive, called "Test & Treat"; demonstrating that a reduction in the time from diagnosis to the start of treatment resulted in higher rates of viral suppression and better adherence to the system (8).

Integrase strand transfer inhibitors (INSTIs) are a group of ARVs, and clinical trials show that INSTI-based regimens result in faster virological suppression compared to other groups, being a great option for the rapid treatment strategy (9). Until now, the only ART capable of that was TAF / FTC / Darunavir / cobicistat, demonstrated in the DIAMOND clinical trial (10). However, there are other co-formulated drugs, active against hepatitis B and that do not require prior analysis to be able to start treatment.

Bictegravir (BIC) is an INSTI marketed in Spain in a single tablet regimen (STR) associated with tenofovir alafenamide / emtricitabine (TAF / FTC); it has a high genetic barrier (therefore it does not need a prior genotypic resistance test to be prescribed) and does not experience differences in effectiveness regarding gender, race, age, CD4 count, or plasma viral load; it is not necessary to perform an HLA study (11).

In certain population groups, these objectives are more difficult to achieve due to their characteristics, low access to healthcare, and low rates of retention in care. People who inject drugs, homeless people, immigrants, and sex workers are vulnerable populations that have a high prevalence of HIV infection and face numerous barriers to accessing healthcare (12,13). To reach the WHO 2030 targets, it is necessary to proactively seek out these vulnerable populations, facilitate their access to HIV therapy, and ensure "retention in care" measures. To achieve this, health services must provide reliable care at every step of the cascade and vulnerable people must continue to attend centers, i.e., be "retained in care." A key point in the cascade is to start or resume antiretroviral therapy as soon as possible to avoid lost opportunities.

In the urban area of Madrid, vulnerable groups gather in specific areas or "hot spots" (shanty towns, homeless shelters, institutions providing social assistance, public zones, and areas where street prostitution is practiced) (14). Vulnerable groups have little access to healthcare and, therefore, do not undergo systematic HIV screening. On the occasions they test positive for HIV, subsequent follow-up in the healthcare system and the possibility of achieving viral load control are scarce, due to the numerous barriers these people find, loss to follow-up, and poor retention in care.

The use of a mobile unit to approach vulnerable populations is essential for a better characterization of risk behaviors and the magnitude of HIV (12–15). The integration of health personnel in mobile units allows for prevention counseling and intervention when necessary. The integration of point-of-care testing as part of HIV "test and treat" strategies in high-prevalence settings can offer an opportunity to improve diagnosis, linkage to care, and access to HIV treatment in vulnerable populations.

A PROM is "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (FDA). They are validated instruments self-completed by patients to record and assess their state of health or well-being. They capture opinions, feelings, and experiences and can measure changes in health status and

quality of life. PROMs are increasingly being used routinely in a series of health services to improve care. They consider patients' subjective opinions as valuable information to evaluate healthcare or the efficacy of conventional medical treatment. They measure aspects of health that are important to patients (16). They contribute to the provision of patient-centered healthcare. Their recording helps demonstrate that patients' experiences are meaningful (17).

There is growing interest in the importance of evaluating the implementation and feasibility of new treatment strategies. Implementation, known as the introduction of an innovation into daily routines; and feasibility, defined as the extent to which a new strategy can be successfully carried out within a given setting, can be assessed by considering the acceptability of the strategy among healthcare professionals and patients.

For all the reasons above, the primary objective of this study is to evaluate the implementation of an approach, screening, and referral strategy using a mobile screening unit in vulnerable populations. All those patients with HIV infection who present detectable PVL (due to recent diagnosis or having abandoned medication) will be offered referral, accompaniment, and same-day medication initiation. The number of participants who achieve an undetectable viral load and whether they remain undetectable for at least 1 year will be evaluated. This strategy of approach, referral, and same-day treatment will likely facilitate retention in HIV care in vulnerable populations. There is experience with this type of strategy in hepatitis C with results that improve cure rates and retention in care in this group of people.

4. Hypothesis

The use of a mobile unit to approach vulnerable HIV-infected individuals with limited access to the healthcare system and initiate/resume ART on the same day ("simplified same-day test and treat strategy") is feasible, effective, and safe, and will allow these individuals to have rapid access to ART and maintain long-term follow-up and HIV healthcare.

5. Objectives

5.1. Primary Objective. To determine if the implementation of an HIV care access and retention model for vulnerable people using a mobile screening unit and a same-day diagnosis and treatment initiation strategy is effective and safe.

5.2. Secondary Objectives. To evaluate the implementation and feasibility of the intervention.

6. Assessment of Trial Endpoints

6.1. Evaluate the effectiveness of the strategy

- Proportion of subjects who agree to participate in the study.
- Proportion of subjects who start ART after inclusion.
- Median time from study inclusion to the start of ART.
- Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at 24 weeks after inclusion.
- Absolute values and changes from baseline in CD4+ cell count and CD4:CD8 ratio at 24 weeks.
- Proportion of subjects who attend visits at weeks 24 and 48.

The efficacy threshold defined for this study is: >80% of subjects included in the study present plasma HIV-1 RNA <50 copies/mL at 24 weeks after inclusion and remain in follow-up and under ART at week 48.

6.2. Evaluate the safety of the strategy

- Incidence and severity of adverse events (clinical and laboratory) up to week 24.
- Incidence of adverse events leading to treatment discontinuation up to week 24.
- Incidence of genotypic resistance mutations in participants with virological failure at week 48.

6.3. Evaluate the implementation of the strategy

- Evaluation of the acceptability, comfort, suitability, usefulness, adequacy, quality, and perceived benefit and satisfaction of the intervention (Appendix 6) at the baseline visit and at the week 24 visit. These parameters will be collected using a scale from 0 to 5.
- To evaluate the implementation of this project, in addition to the aspects in the previous point, the aforementioned endpoints will be used (Evaluate the effectiveness of the strategy and Evaluate the safety of the strategy).

7. Definitions

Mobile Screening Unit (MSU): The mobile screening unit consists of a van adapted with a consultation and laboratory space, a satellite car (DAS service) for deliveries or referrals, and a socio-sanitary team.

DAS Service: Referral, accompaniment, and follow-up service (*Servicio de derivación, acompañamiento y seguimiento*). Formed by an educator and a car owned by Fundación SEIMC-GESIDA to perform the accompaniments. This service is also available to healthcare professionals (infectious disease specialists, hepatologists, and addiction doctors) who need to refer patients with HCV/HIV infection within the Community of Madrid.

Vulnerable Persons (VP): Subjects without economic resources who, due to their characteristics, are in an unfavorable situation to access screening, diagnosis, and treatment of HIV infection, and in whom this situation may lead to a problem for their individual health and public health.

Hot spots: Places where VP concentrate or places where the prevalence of VP is high according to data obtained in previous screenings. The hot spots identified to date are the following: Shanty towns (Cañada Real Galiana…), harm reduction mobile units (SMADS, located in Cañada Real, and Madroño, located in Prado del Rey street), homeless shelters, immigrant centers, detoxification or rehabilitation centers, addiction centers of the city council and other organizations/institutions, places where prostitution is practiced (Marconi industrial estate), public places where VP concentrate on the street, squares, boulevards, illegal settlements, and landfills.

Virological Failure (VF): Virological failure is defined as an HIV-1 RNA ≥50 copies/mL followed by a second HIV-1 RNA assessment ≥200 copies/mL.

Adverse Event (AE): Any untoward medical occurrence in a participant in a clinical investigation, temporally associated with the use of a trial treatment, whether or not considered related to it. Therefore, an adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a trial treatment, whether or not related to the trial treatment.

8. Methodology

8.1. Study Design

Pilot, prospective, single-center study with a single treatment arm. Phase IV.

8.2. Duration

The study will last 12 months. Participant inclusion and follow-up visits will be conducted every working day according to the working calendar for the years 2022 and 2023. From Monday to Friday and, preferably, during morning hours (8:00h-15:00h). The possibility of intervening at other times is contemplated to contact people who attend certain resources or locations outside the generally established hours. All participants will be followed for a maximum duration of 48 weeks after the start of treatment. A period of 10 days will be allowed from the screening visit to the treatment initiation visit.

8.3. Population to be screened

Vulnerable populations (see definitions). VPs include:

- Drug users (including alcohol).
- Homeless people.
- Sex workers.
- Undocumented immigrants.
- Refugees. Applicants for international protection.
- Men who have sex with men.
- People in dual pathology centers, psychiatric or mental health centers.
- Others.

8.4. Location

The project will be carried out in the Autonomous Community of Madrid. Using the MSU, the places where the previously described VPs concentrate will be accessed. These places will be called “hot spots.” The study will be conducted in a hospital center, where visit procedures will be performed, blood samples processed, and trial medication dispensed. Additionally, recruitment and the selection visit for study participants will be conducted in a mobile unit operating in Madrid.

8.5. Staff and Research Team

8.5.1. Medical Team

Formed by the physicians from the hospital's HIV clinic and the MSU physicians. As principal investigators and/or sub-investigators, their main functions will be to inform potential candidates about the trial, sign informed consent, perform a correct medical history and physical examination, verify inclusion/exclusion criteria, review concomitant medication and adverse events (AE), and prescribe trial medication or other concomitant medication.

8.5.2. Nursing Staff

The nursing staff will be responsible for blood sample collection and subsequent processing. They will perform finger pricks for whole blood extraction and rapid testing (HIV and hepatitis C screening). In cases where rapid tests are positive, a new finger prick will be performed for HIV or hepatitis C virus (HCV) RNA analysis using Xpert in the MSU. In the included participants, they will perform blood extraction via venipuncture and subsequent processing according to protocol procedures. They will take the participants' vital signs. Finally, they will produce a brief report for the participant including health education.

8.5.3. Social Worker

Will have knowledge and mastery of the homeless network and the drug dependency network. Will be responsible for administering questionnaires to the participant and performing a social assessment. Activities aimed at the effective management and application of existing resources, to ensure that the attended subjects are able to resolve conflicts arising from their vulnerability status. In cases where referral to a health center is required, they will organize accompaniments and coordinate with the different services and hospital health personnel. They will be in charge of requests and management of permits and authorizations. They will detect cases of vulnerability and abuse/violence and direct them to the respective instances. They will perform support tasks for the nursing staff and educator for the subsequent individualized follow-up of users in the referral phase, health follow-up, and supervision of treatment adherence. Finally, they will be responsible for completing the e-CRF along with the rest of the investigators.

8.5.4. Educator

Their responsibilities include: Active recruitment of users, health education intervention, prevention and socio-sanitary “Counselling” during testing, dissemination of the project in homeless and drug dependency networks, coordination with the nurse and social worker of the mobile team for the subsequent individualized follow-up of users in the referral phase, health follow-up, and supervision of treatment adherence. In cases where referral is required, they will perform accompaniments and coordinate with the different services and teams. Collaborate with requests and management of permits and authorizations. They will be the MSU driver. They will perform support tasks for the medical staff, nursing, and social worker.

8.6. Mobile Screening Unit

The mobile unit uses two vehicles. A van with health authorization adapted for this project and a satellite car.

8.6.1. Van

This vehicle has two seats (driver and passenger) and is divided into two areas (Appendix 1, Figure 1); 1) Consultation area where the evaluation by the research

team is performed and 2) A laboratory, where the rapid test, blood extraction, sample processing, and diagnosis are performed. It has different storage spaces for the material necessary to carry out the study, solar panels, and an awning. The awning expands the intervention space to the exterior of the vehicle, improving the visibility and accessibility of the device. Additionally, there is a physical examination area (stretcher), a sink, and a refrigerator and centrifuge for the conservation and processing of biological samples.

8.6.2. Satellite Car

The satellite vehicle is a car currently used to provide coverage for the DAS Service (see definitions). it is provided with comprehensive insurance and maintenance throughout the project period. The satellite vehicle will be used for transportation to different health centers for all those subjects who require it, i.e., those who have a positive rapid test or PCR and have difficulties accessing the health system to receive antiviral treatment (Appendix 1, Figure 2). This vehicle will also be used to transport samples from the MSU to the hospital.

8.6.3. Operation of the MSU

The MSU has been operating since 2019 in the Community of Madrid and has several agreements with different organizations and institutions that facilitate HIV and hepatitis C screening in VP. The MSU has its operational base in Calle Antonio López (Madrid), a center currently used by the association Madrid Positivo. From the base, the locations for the approach, screening, and recruitment of study participants will be planned in advance. The research staff requests permits from the relevant institutions or centers to carry out the intervention. An active search for VP is performed in the Community of Madrid, prioritizing locations where these populations concentrate. For this, a flexible and dynamic screening with real-time analysis of the database is used. The usual procedure of the MSU is to perform a rapid HIV and hepatitis C test on all users. In cases with a positive rapid test for hepatitis C, infection activity is confirmed using GeneXpert®. In cases with a positive rapid test for HIV, infection is confirmed using the GeneXpert® Qual test and subsequently, the HIV viral load is analyzed using GeneXpert® Cuanti. As a matter of course, people who have undergone HCV and HIV screening and have confirmed active infection via PCR are offered referral and accompaniment to a hospital center. For this clinical trial, all persons who have undergone screening/diagnosis and meet the inclusion criteria for the trial will be offered participation in the study.

8.6.4. Permits

Both for the intervention on the street and within the previously described centers, written permission from the responsible institutions (City Council, SERMAS, and other organizations) will be required. The MSU team will be responsible for requesting all necessary permits in advance.

8.6.5. Itinerary

An itinerary with the intervention locations will be established. This itinerary or route will be subject to changes according to permits and pending work from previous days. Flexibility in the itinerary will be allowed, adjustable to the calendar, in order to adapt the mobile unit to the routines of greatest influx at the different stops, having the capacity to modify routes to attend hot spots on the days and times of greatest influx. The team may perform a prior reconnaissance of the hot spots. The itinerary can be accessed through the project's website: www.unidadmovil.es.

8.7. Referrals

All patients who have signed the informed consent and present a positive rapid HIV or HCV test result and also present data of viral activity (positive PCR for hepatitis C and quantitative positive PCR for HIV) will be offered a referral to a health center for assessment. Likewise, accompaniment will be offered through study personnel and using the DAS Service. The educator accompanying the patient to the hospital will be responsible for accompanying the participant to the specialist's consultation and to collect the medication at the Pharmacy service.

8.8. Biological Sample Procedures

8.8.1. Finger-prick Blood Draw

The procedure will be performed with a lancet to obtain whole blood. The following studies can be performed with the sample:

- Rapid HIV and HCV tests.
- On-site HIV and HCV PCR using GeneXpert.

8.8.2. Venipuncture Blood Draw

Blood will be obtained by venipuncture to perform the trial laboratory procedures. Venipuncture blood draw can be performed at the hospital or in the MSU. When the draw is performed in the MSU, samples will be sent on the same day to the hospital for subsequent labeling, processing, and analysis.

8.8.3. Sample Centrifugation

The MSU has a centrifuge to centrifuge samples extracted by venipuncture to perform GeneXpert quantitative PCR analysis and quantify the HIV viral load. In selected cases, blood samples obtained by venipuncture may also be centrifuged for trial laboratory procedures.

8.8.4. Urine Sample

A urine sample will be collected to perform the pregnancy test for women of childbearing age, according to the trial procedures.

8.9. HIV Screening and Diagnosis

8.9.1. Rapid Tests

Rapid tests will be performed for HIV, hepatitis C, B, and syphilis screening. Commercial brands available during the study will be used.

8.9.2. On-site PCR Performance

All positive results will be confirmed within minutes using an in situ PCR (Xpert® HIV-1 Qual) in the mobile unit. Xpert Qual is a qualitative test that provides on-site and on-demand molecular testing for early diagnosis. It is based on GeneXpert technology. For PCR tests with GeneXpert, 100µl of capillary blood will be collected using a minipipette or 1 dried blood spot sample on paper (60-70 µl) in cases of Xpert HIV-1 Viral Load. The PCR test will be performed immediately on-site and results will be returned within minutes (60-93 minutes run time).

- **Xpert HIV-1 Qual:** a qualitative test providing on-demand molecular testing for early diagnosis. Based on GeneXpert technology, Xpert HIV-1 Qual provides a nucleic acid-based test for RNA and proviral DNA in a fully integrated cartridge. The limit of detection of the HIV-1 Qual test is 278 copies/mL for whole blood samples and the limit of detection for DBS samples is 668 copies/mL.
- **Xpert HIV-1 Viral Load:** a quantitative test allowing for on-demand molecular determination. Based on GeneXpert® technology, the Xpert HIV-1 Viral Load test automates the analysis process, including extraction, purification, and reverse transcription of RNA and real-time quantification of cDNA, in a single fully integrated cartridge. The process lasts 91 minutes with minimal handling time.
- **Xpert HCV VL Fingerstick:** on the GeneXpert® system: Rapid diagnosis of HCV RNA from both venous and capillary whole blood samples. Quantitative RNA results available in less than 1 hour at the point of care.

8.10. Treatment.

Patients included in the study who access the HIV consultation will start treatment with BIKTARVY on the same day of inclusion. The medication will be provided by the sponsor, and dispensing will be carried out through the pharmacy service. Medication dispensing may be performed in a delegated manner, i.e., a member of the research team collects the medication from the pharmacy and subsequently delivers it to the patient outside the hospital environment. It will be recorded whether the dispensing was in-person or delegated. Study medication will be delivered to participants or the delegated person. Medication delivery will be bimonthly; therefore, two bottles of medicine will be delivered.

8.11. Follow-up.

Blood tests will be performed at weeks 4, 12, 24, and 48 after study inclusion. PROMs and PREMs will be performed at baseline and at week 24. Contact will be established by telephone. The mobile unit team will be responsible for contacting the patient at all visits (4, 12, 24, and 48) and will coordinate with the laboratory

(blood analysis), the hospital pharmacy (adherence and delivery of ART), and the patient (PROMs/PREMs, see Appendix 5 and 6). For the PREM, a non-validated questionnaire will be administered with questions agreed upon by the mobile screening unit team that regularly attends to vulnerable populations, such as drug users, homeless people, people with alcohol dependency, etc.

9. Study Design

9.1. Sample Size

For the sample size calculation, data from a 2019 study were taken into account. In that study, the same procedure was used (approaching VP through a mobile screening unit), but in that case, patients with active hepatitis C infection without antiviral treatment were diagnosed and referred to hepatology and infectious disease consultations. The objectives were to evaluate the implementation of this strategy, the cure rate, and the retention in care of this group. Globally, the proportion of people who achieved a sustained viral response and remained in follow-up was 70% (14).

With these data, we have calculated that a random sample of 100 individuals is sufficient to estimate, with 95% confidence and a precision of +/- 10 percentage units, a population percentage that is expected to be around 70%. The necessary replacement percentage is anticipated to be 20%.

9.2. Treatment Plan:

Participants will receive a single oral dose of BIC/FTC/TAF every day for 12 months.

- Bictegravir (BIC) 50 mg
- Emtricitabine (FTC) 200 mg
- Tenofovir alafenamide (TAF) 25 mg

9.3. End of Study

The study completion date will be the date of the last visit of the last participant who completes the week 50 study completion visit.

10. Trial Population

Participants must meet all inclusion criteria and none of the exclusion criteria at the time of screening.

10.1. Inclusion Criteria.

Screening will be performed consecutively on adults (over 18 years of age) who approach the MSU. Those who meet the inclusion criteria will be invited to

participate in the trial. No participant will be excluded based on race, gender, origin, or sexual orientation. Participants wishing to participate in the study must meet all the criteria listed below:

1. Vulnerable person ≥18 years old.
2. Understand and sign the informed consent.
3. Confirmed HIV infection.
4. Not receiving ART or being on ART with PVL >1000 copies/ml.

10.2. Exclusion Criteria.

Participants presenting any of the following criteria may not participate:

1. Inability to provide contact data.
2. History of allergy to any of the following drugs: bictegravir, tenofovir alafenamide, or emtricitabine.
3. Taking antiretroviral treatment for less than 1 month.
4. Pregnancy or breastfeeding at the time of screening or gestational desires during the study period.
5. Suspicion or diagnosis of active opportunistic disease.
6. History of severe liver disease (Child-Pugh C) or history of decompensated liver disease (defined as the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice).
7. History of renal disease CKD-EPI <30ml/min.
8. Presenting any condition that, in the investigator's opinion, makes the patient not a candidate for inclusion (Active disease, social situation, intoxication…).

10.3. Restrictions

See section 11.4. (Prohibited medications and non-pharmacological therapies).

10.4. Withdrawal/Discontinuation of Treatment/Trial

Participants may be withdrawn from the study at any time, without prejudice to their future medical care. The participant may discontinue study treatment or withdraw from the study at their own request; at the investigator's clinical discretion; at the sponsor's request; or if the withdrawal criteria indicated below are met: The following points may lead to the discontinuation of trial treatment:

- Pregnancy (Appendix 3 and 4). Study treatment must be discontinued during pregnancy.
- Withdrawal of informed consent.

- The investigator considers that, for safety reasons, it is in the participant's best interest to discontinue treatment.
- Adverse event resulting in death.
- Certain adverse events (see Appendix 2).
- Loss to follow-up.
- Discontinuation and termination of the trial by the sponsor.

Every effort will be made to keep participants in the study. Whenever possible, all patients who prematurely stop participating during any period of the study will undergo the evaluations designated for early withdrawal. The reasons why participants do not complete the study will be recorded in the e-CRF. Virological failure (VF) is not a criterion for discontinuation.

11. Treatment

11.1. Study Treatment

Study intervention: Patients will start antiretroviral treatment at the baseline visit (V1). Experimental treatment: Bictegravir/Emtricitabine/Tenofovir alafenamide in a single tablet (STR).

- Dose: Bictegravir 50 mg/Emtricitabine 200 mg/Tenofovir alafenamide 25 mg
- Route of administration: oral
- Administration schedule: once daily for 48 weeks. The tablets are purplish-brown, capsule-shaped, and film-coated, debossed with "GSI" on one side and "9883" on the other. Each bottle contains 30 tablets (NDC Package Code: 61958-2501-1 Biktarvy), a silica gel desiccant, a polyester coil, and a child-resistant closure. Each tablet contains 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). Tablets should be stored below 30 °C.

11.2. Adherence to Treatment

During the study, treatment compliance will be monitored through follow-up visits using the SMAQ questionnaire (Appendix 7), and all information will be recorded in the appropriate section of the e-CRF. Patients will be instructed to bring the remaining study treatment during each visit for review and verification of the number of remaining drug tablets. This procedure will be performed by the MSU research team.

11.3. Prior, Concomitant, and Subsequent Treatment

All concomitant medications taken by the patient at the screening visit, including ART (if taken), will be recorded in the participant's e-CRF. The minimum requirement is to record the name of the medication and the dates of

administration. This will include all prescription drugs, herbal products, vitamins (e.g., vitamin D), minerals (e.g., calcium supplements), and over-the-counter medications. Any changes in concomitant medication will also be recorded in the participant's e-CRF. Any concomitant medication deemed necessary for the participant's well-being during the study may be administered at the investigator's discretion, unless listed as a medication of special consideration due to the risk of interactions (Section 11.4). However, it is the investigator's responsibility to ensure that details regarding medication are recorded in full in the e-CRF. The sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

11.4. Medications and Non-pharmacological Therapies of Special Consideration.

All concomitant medications taken by the patient at the screening and follow-up visits will be recorded in the participant's e-CRF. Prohibited drugs or non-pharmacological therapies are detailed below:

- Supplements or multivitamins containing calcium, iron, or magnesium should not be taken concomitantly with study therapies under fasting conditions. The general recommendation is to take them 2 hours after or 6 hours before study therapies.
- The following medications or their equivalents may significantly reduce BIC blood levels and, therefore, should not be administered simultaneously with BIC: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin, Rifapentine, or Rifampin.
- Refrain from excessive consumption of St. John's Wort alongside BIC, as it may significantly reduce BIC blood levels.

11.5. Packaging and Labeling of the Investigational Medicinal Product

. The study treatment will be provided by the study center. Study treatments will be labeled in accordance with applicable regulatory requirements and any other regional or local requirements.

11.6. Handling, Storage, and Accountability

Only participants included in the trial may receive the study treatment and only authorized center personnel may supply or administer the trial treatment. All trial treatments must be stored in a secure, environmentally controlled, and monitored (manually or automated) location in accordance with the labeled storage conditions, with limited access to the investigator and authorized center personnel. The investigator, the institution, or the medical institution director (where applicable) is responsible for the trial treatment accountability, reconciliation, and record-keeping (i.e., records of receipt, reconciliation, and final disposition).

11.7. Treatment and Care After Completion of the Study

Subjects who successfully complete the 48 weeks of treatment may continue to receive the assigned treatment (through the local program). Viral failure is defined as an HIV-1 RNA ≥50 copies/mL followed by a second consecutive evaluation of HIV-1 RNA ≥200 copies/mL. If any plasma HIV-1 viral load result is ≥ 50 copies/mL, the plasma viral load test must be repeated 2-4 weeks later to confirm viral failure.

12. Study Evaluations and Procedures

Before performing any study procedure, all potential participants will sign an informed consent (IC) form. Participants will have the opportunity to have any questions answered before signing the IC. The investigator must answer all questions raised by the participant. The investigator or designee will also sign the IC.

12.1. Variables

Age, sex at birth, race, medical history, drug use (alcohol, heroin, cocaine, recreational drugs). Active use. Homelessness. Economic income, contact with relatives, stable housing. Follow-up by health center. Previous follow-up in HIV unit. Last negative HIV serology. Date of HIV diagnosis, CDC stage, CD4 nadir, baseline PVL. Most likely route of transmission, current ART, prior ART, ART start date, prior virological failures, prior discontinuations. Documented resistance to ART. Weight, height, physical examination. Laboratory: • Complete blood count: hemoglobin and platelets. • Biochemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, glomerular filtration rate (GFR). • Immunology: CD4+ lymphocytes and CD8+ lymphocytes. • Virology: Quantification of HIV-1 RNA. An HIV-1 RNA assay with a lower limit of detection (LLOD) of 30 copies/mL will be used. In cases of patients with a positive rapid test or serology for hepatitis C, an HCV RNA viral load will be performed. • Urine: Pregnancy test. Participant agrees to be referred. Attends consultations. Starts/resumes medication. Adherence to appointments. Evaluation of ART adherence since the last visit. Missed doses reported by the patient. Has the count of medication returned by the patient been performed? Adverse event: Is it a hepatic event? Start date, continuous, AE, SAE, Severity, Outcome, Related to study drug, Action taken. Has the patient discontinued or been withdrawn from the study prematurely? Date of discontinuation or withdrawal? Reason for termination, Loss to follow-up, Death? Cause of death.

12.2. Study Visits 4.2.1. Screening Visit (day -10 to day 0)

Screening evaluations will be performed for all potential participants to determine study eligibility. The following procedures must be completed within 10 days prior to the date of the first dose of study treatment administration on day 0:

- Obtain informed consent from the participant.
- Review inclusion and exclusion criteria.

- Collect relevant demographic and medical history information.
- Perform a complete clinical examination (Section 12.2.1).
- Review prior and concomitant medication.
- Monitor SAEs (from the time the participant signed the IC).
- Perform a serum/urine pregnancy test (only for female participants and document contraceptive methods).
- Collect blood samples for screening evaluations as indicated in the Schedule of Evaluations and Procedures (See Section). See also section (Clinical laboratory analysis).

12.2.2. Baseline Visit (day 1, week 0)

The first dose of study treatment will be administered at the baseline visit (week 0). The following procedures must be performed prior to administration:

- Review inclusion and exclusion criteria.
- Perform a urine pregnancy test (only for female participants).
- Review concomitant medications.
- Monitor AEs. Once eligibility is reconfirmed, the following procedures must be performed:
- Perform a targeted clinical examination (Section 12.2.1).
- Collect blood samples as indicated in the corresponding Flow chart.
- Administer the PROMS questionnaire (HADS and WHOQOL-BREF QUALITY OF LIFE SCALE) and PREMS (see Appendix 5 and 6).
- Consumption of other drugs and menstrual status will be recorded.
- Administer the assigned treatment.
- Provide participants with study treatment.
- Provide the schedule of study procedures. The screening visit and baseline visit may coincide on the same day.

12.2.3. Subsequent Visits (weeks 4, 12, 24, and 48)

Allowed window of -5 to +5 days for week 4; Allowed window of -15 to +15 days for weeks 12, 24, and 48. See Flow chart for more detail. The following procedures must be performed:

- Review concomitant medications.
- Monitor AEs.
- Alcohol intake, drug use, and menstrual status (for women of childbearing age) will be recorded.

- Collect data on social situation.
- Perform a targeted clinical examination (Section 12.2.1).
- Collect blood samples as indicated in the section.
- Perform a urine pregnancy test (only for female participants).
- Hepatitis C rapid test.
- SMAQ Adherence Questionnaire (Appendix 7) and drug accountability.

12.2.4. Safety Follow-up Call/Visit

A telephone call will be made to collect information on safety issues 15 days after the last dose of study treatment. The allowed window is -10 to +10 days. Patients will be asked about potential adverse events and concomitant medication. If the investigator deems it appropriate or necessary, patients will come to the center for an in-person safety visit. In this case, in addition to asking about potential adverse events and concomitant medication, vital signs will be collected, a physical examination will be performed, and blood will be collected for laboratory analysis.

12.2.5. Early Withdrawal Visit

The following procedures must be performed:

- Review concomitant medication.
- Monitor AEs.
- Reason for early withdrawal.
- Genotype-resistant mutation study in case of virological failure.

12.3. Study Evaluations 4.3.1. Physical Examination

Comprehensive or targeted physical examinations will be carried out as indicated in the Flow chart. When scheduled at the same visit, vital signs measurements must be performed before the collection of any blood or other samples. A complete physical examination will include height, weight (using precision scales for weight control), and evaluation by systems: skin; head, eyes, ears, nose, and throat; respiratory system; cardiovascular system; abdomen (liver, spleen); and lymph nodes.

12.3.2. Clinical Laboratory Analysis

Samples for hematology and biochemistry will be collected at the times specified in the Flow chart. Any abnormal laboratory test results (hematology or clinical chemistry) considered clinically significant by the investigator will be recorded as an AE or SAE as specified in Section 13.12. Samples will be analyzed at the study center and in the local laboratory. The laboratory tests performed during the study will be as follows:

- **Complete blood count**: hemoglobin and platelets.

- **Biochemistry**: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, glomerular filtration rate (GFR).
- **Immunology**: CD4+ lymphocytes and CD8+ lymphocytes.
- **Virology:** Quantification of HIV-1 RNA. An HIV-1 RNA assay with a lower limit of detection (LLOD) of 30 copies/mL will be used. In cases of patients with a positive rapid test or serology for hepatitis C, an HCV RNA viral load will be performed.
- **Urine**: Pregnancy test.

12.3.3. Genotypic Resistance Mutations (in case of viral failure).

If any plasma HIV-1 viral load result is ≥ 50 copies/mL, the plasma viral load test must be repeated 2-4 weeks later to confirm viral failure. If VF criteria are met, a plasma sample from the initial test and the confirmatory high viral load at the time of virological failure will be analyzed for resistance study performance. In case of viral failure, genotyping must be performed to detect viral resistance mutations emerging to treatment, and appropriate ART should be considered at the investigator's discretion.

13. Adverse Events (AE)

Participants will be monitored to detect any AE from the signing of the informed consent until the study completion visit. Adverse events for participants who do not pass screening will be recorded in the source data. The investigator or a medically qualified designee will review each event. The investigator or a sub-investigator will evaluate its relationship with the study drug. Each sign or symptom will be graded according to its severity, and the date and time of onset, cessation, and resolution will be recorded. The treatment of any adverse reaction will be evaluated and managed by a physician, either at the MSU or in the emergency room of a nearby hospital, as appropriate.

13.1. Events that meet the definition of an AE

- Any abnormal laboratory test result (hematology, chemistry, or urinalysis) or other safety evaluations (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, which are considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to the progression of the underlying disease).
- Exacerbation of a pre-existing chronic or intermittent condition, including an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after the administration of the study intervention, even if they were present before the start of the study.
- Signs, symptoms, or clinical sequelae of a suspected drug interaction.
- Signs, symptoms, or clinical sequelae of a suspected overdose of the study intervention or a concomitant medication. Overdose *per se* will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-destructive intent. Such overdoses must be reported regardless of the sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" *per se* will not be reported as an AE or SAE. Such cases will be collected in the efficacy evaluations. However, signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they meet the definition.

13.2. Events that DO NOT fit the definition of an AE

- Any abnormal clinically significant laboratory finding or other abnormal safety evaluations associated with the underlying disease, unless the investigator considers them more severe than expected for the participant's condition.

- The disease/disorder under study or expected progression, signs or symptoms of the disease/disorder being studied, unless they are more severe than expected for the participant's condition.
- Medical or surgical procedures (e.g., endoscopy, appendectomy): unless the condition leading to the procedure is the AE.
- Situations where no adverse medical event occurred (hospital admission for convenience or social reasons).
- Predicted daily fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

13.3. Serious Adverse Event (SAE) If an event is not an AE according to the previous definition, then it cannot be an SAE even if the conditions of seriousness are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to disease progression). An SAE is defined as any adverse medical event that, at any dose:

- Results in death.
- Is life-threatening (any event in which the participant is at risk of death at the time of the AE; it does not refer to an event that hypothetically could have caused death if it were more severe).
- Requires hospitalization or prolongation of existing hospitalization; in general, hospitalization means the participant has been admitted (usually involving at least one night's stay) to the hospital or emergency room for observation and/or treatment that would not have been appropriate in a medical office or outpatient setting. Complications occurring during hospitalization are AEs. If a complication prolongs hospitalization or meets any other severity criteria, the event is serious. In case of doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen is not considered an AE.
- Results in persistent or significant disability/incapacity; the term disability means a substantial disruption of a person's ability to carry out normal life functions. This definition is not intended to include experiences of relatively minor medical importance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., a sprained ankle) that may interfere with or prevent daily life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect; or is a medically important event.
- Other situations: Medical or scientific judgment should be exercised to decide if the notification of an SAE is appropriate in other situations, such as important medical events that may not be immediately life-threatening or

result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. Generally, these events should be considered serious. Examples include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or seizures not resulting in hospitalization, or the development of drug dependency or drug abuse.

The following special situations must also be considered and reported as an SAE:

- All events of ALT 3xULN and bilirubin 2xULN (>35% direct bilirubin) or ALT 3xULN and INR > 1.5, if INR is measured, which may indicate severe liver injury.

13.4. Attribution/Causality

- The investigator is obligated to assess the relationship between the trial treatment and each of the AE/SAEs.
- The investigator will use their clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant treatment, and other risk factors, as well as the temporal relationship of the event to treatment administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or the approved local prescribing information in their assessment.
- For each AE/SAE, the investigator must document in the medical notes that they have reviewed the event and provided a causality assessment.
- There may be situations where an SAE has occurred and the investigator has minimal information for the initial report to the sponsor/designee. However, it is essential that the investigator always assesses causality for each event before reporting SAE data.
- The investigator may change their opinion on causality considering follow-up information and submit a follow-up SAE report with the updated assessment.

13.5. Grading of Attribution/Causality of Adverse Effects

- **Related:** An adverse event where there is a reasonable possibility of a causal relationship with the use of the study drug. "Reasonable possibility" means there are facts/evidence or arguments suggesting a causal relationship. Facts/evidence supporting this include, for example, a temporal relationship, a pharmacologically predicted event, or a

dechallenge/re-challenge. Confounding factors, such as concomitant medication, concurrent illness, or relevant medical history, must also be considered.

- **Not related:** An adverse event that is not related to the use of the drug.

13.6. Intensity The intensity of an AE refers to the extent to which an AE affects the participant's daily activities. The investigator will assess the intensity using the DAIDS grading table version 2.1, March 2017, and assign it to one of the following categories:

- **Mild:** No or minimal interference with usual social and functional activities.
- **Moderate:** Greater than minimal interference with usual social and functional activities.
- **Severe:** Inability to perform usual social and functional activities. A "severe" AE should not be confused with an "SAE." Severe is a category to grade intensity; both AEs and SAEs can be graded as severe.
- **Life-threatening:** Inability to perform basic self-care functions.

Changes in severity must be documented to assess the duration of the event at each intensity level. Intermittent AEs do not require documentation of the onset and duration of each episode. The term "severe" is often used to describe intensity, while "serious" is based on outcome criteria.

13.7. Suspected Unexpected Serious Adverse Reactions (SUSAR)

- A Serious Adverse Reaction (SAR) that is unexpected or whose development is uncommon (unexpected event) observed during a clinical trial and for which there is a relationship with the study drug.
- These reactions must be reported immediately according to national legislation and international guidelines.
- The sponsor will inform the competent authorities of the applicable autonomous communities of any SUSAR that may be related to the study treatment.
- In this study, the reference safety information (RSI) will be the Summary of Product Characteristics (SmPC) for the study drug (Biktarvy®).

13.8. Reporting of Adverse Events

Care will be taken not to introduce bias in the detection of AEs and/or SAEs. The preferred method is open-ended verbal questions to study participants. All SAEs will be collected from the signing of the informed consent until the follow-up visit.

AEs will be collected from the first dose until the follow-up visit. Participants will be asked about their well-being, hospitalizations, accidents, or changes in medication at each visit. AEs identified from laboratory data or physical exams will be documented in the e-CRF.

13.9. Notification of Serious Adverse Events

The investigator must notify any SAE to the sponsor immediately (within 24 hours of becoming aware of the event). The report must include study name, investigator data, participant number, clinical description, treatment details, causality, and whether it was fatal. The investigator must fill out and sign the SAE report form (Appendix 2) and email it to: **pharmacovigilance@f-sg.org**.

13.10. Accelerated SUSAR Reporting

The sponsor will notify all suspected SUSARs to the AEMPS and health authorities within 15 calendar days (or 7 days if fatal/life-threatening). All AEs, including SAEs, will be followed until resolution or stabilization. Investigators are not required to actively seek AEs in former participants, but must report any "late" events they become aware of that are reasonably related to the trial.

13.11. Follow-up of Adverse Events

All AEs will be followed until clinical resolution, stabilization, or the end of the follow-up period. Long-term AEs may be handed over to the treating physician with the agreement of the sponsor's medical monitor. The investigator is obligated to perform supplementary measurements if medically indicated to elucidate the nature/causality of the event.

13.12. Clinical Laboratory Adverse Events

Changes in laboratory results considered clinically significant by the investigator will be reported as AEs. The investigator must review all laboratory tests and sign the reports. If an abnormal value is determined to be a clinically significant change from baseline, it is considered an AE.

13.13. Contraception and Pregnancy

Women of childbearing age must use effective contraception according to CTFG recommendations.

- **Highly effective methods (<1% failure):** Implants, IUDs, hormone-releasing systems, bilateral tubal occlusion, or vasectomized partner. Also

combined hormonal contraception (oral, intravaginal, transdermal, injectable) and progestogen-only hormonal contraception associated with inhibition of ovulation, or sexual abstinence.

- **Acceptable methods:** Progestogen-only oral contraception (without ovulation inhibition), male/female condoms with/without spermicide, cervical caps, diaphragms, or sponges with spermicide.

Participants must notify the investigator immediately if they become pregnant. Pregnancy is not considered an AE/SAE unless there is a suspicion that the investigational product interfered with contraceptive efficacy. Pregnancies must be followed until the outcome (birth, elective termination, or miscarriage). All neonatal deaths within 28 days of birth must be reported as SAEs regardless of causality. If pregnancy is confirmed, the participant may be offered treatment with **raltegravir (RAL)** twice daily and **tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)** once daily, following the product datasheets.

14. Records Management

14.1. Data Collection

Data will be collected using an electronic source. The data management plan will specify for which evaluations data will be collected through RedCAP. All relevant pages of the e-CRF must be completed for each participant based on the visits attended. In the case of participants who did not pass screening, the version and date of the signing of the informed consent form, and the Inclusion and Exclusion Criteria not met, will be recorded separately. For participants who withdraw prematurely, all visits attended by the participant must be completed, including withdrawal and follow-up visits. If a participant withdraws from the study, the reason must be noted in the e-CRF. The e-CRF must be completed on an ongoing basis. Designated investigator staff will enter the data required by the protocol into the e-CRF. Designated research center staff will not have access to the electronic data capture system until they have received training. The investigator must certify that the data entered into the e-CRF are complete and accurate. Once the e-CRF has been declared complete and accurate, the e-CRF will be locked following written approval from the Sponsor. Any changes to the e-CRF from that moment on require a database unlock and may only be carried out after receiving written approval from the Sponsor.

14.2. Source Documents

Source documents are defined as all information in original records and certified copies of originals of clinical findings, observations, or other activities of a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents will include, but are not limited to, progress notes, test records, and data recorded from automated instruments. Investigators will retain all source documents relating to this trial. The investigator must allow monitoring, audits, review by the Independent Ethics Committee (IEC/EC), and regulatory inspections that provide authorized personnel with direct access to source documents, including documents necessary to confirm inclusion/exclusion and relevant patient records while participants are receiving treatment in the trial.

14.3. Management of Files at the Trial Site

It is the responsibility of the investigators to ensure that the trial site files are maintained in accordance with the International Guidelines for Good Clinical Practice and the ethical principles originating in the Declaration of Helsinki.

14.4. Record Retention at the Trial Site

The investigator is obliged to retain the trial records and data for safety reasons and for auditing and inspection following the completion of the trial. The legislation applying to the custody period of the master file since the entry into force of RD 1090/2015, of December 4, is its Art. 43, according to which: "1. The clinical trial master file shall comply with the provisions of Articles 57 and 58 of Regulation (EU) No. 536/2014 of the European Parliament and of the Council, of

April 16, 2014. Its content shall take into account the supplementary guidance published by the European Commission in this regard. 2. The sponsor and the investigator shall retain the content of the master file in paper or digital format for each clinical trial for at least twenty-five years after the completion of the trial, or for a longer period if required by other applicable requirements." The investigator must notify the sponsor/recipient before destroying any records related to the trial.

15. Statistical Methods

15.1. General Aspects

The essential aspects to be considered when creating the statistical analysis plan for this study are described below in general terms. Once the trial is finalized and all possible data discrepancies have been resolved by the investigators, the study database will be closed and transferred to the coordinating investigator, who will be responsible for the statistical analysis. A detailed analysis plan will be prepared and approved by the sponsor to guide the data analysis and justify any changes from the original plan. A general descriptive analysis of the variables included in the study will be performed. Absolute and relative frequency distributions for qualitative variables will be presented, as well as measures of central tendency and dispersion (mean, standard deviation, median, minimum, and maximum) for quantitative variables. 95% confidence intervals (CI) will be presented for results associated with the primary objective and the main secondary variables. Erroneous or non-recoverable missing data will not be imputed and will be left as missing for both the primary and secondary objective analyses. When inferential analysis is required, parametric tests will be used for continuous variables and non-parametric tests for ordinal, categorical, or non-parametric variables. The hypothesis tests used will be two-sided in all cases with a significance level of 0.05. For variables that do not fit a normal (or parametric) distribution, Mann-Whitney (for unpaired data) or Wilcoxon (for paired data) hypothesis tests will be used. In the analysis of contingency tables, as well as for the comparison of proportions and/or frequency distributions, the Chi-square test or Fisher's exact test will be used, as appropriate. A flowchart of the study patients will be included, including the number of patients included (eligible), the number of patients who withdrew from the study, and the reason for withdrawal/dropout. A table with the socio-demographic and clinical characteristics of the patients will be presented. The clinical characteristics to be presented in said table include patient and disease data, including their virological and immunological status.

15.2. Populations for Analysis

The following populations are defined in the study:

- **Included Population:** consisting of all patients included in the study who have signed the informed consent. It will be used to analyze the proportion of subjects who agree to participate in the study and the proportion of subjects who start ART after inclusion.

- **"Intent-to-Treat" (ITT) Population:** consisting of all patients included in the study who have received at least one dose of the study treatment. The proportion of subjects who complete visits at weeks 24 and 48, the median time from study inclusion to the start of ART, and the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at 24 weeks from inclusion will be measured.
- **"Per Protocol" (PP) Population:** consisting of all patients who have received at least one dose of the study treatment and excludes those patients withdrawn from the study due to major protocol deviations. The proportion of subjects with plasma HIV-1 RNA <50 copies/mL at 24 weeks from inclusion, absolute values and changes from baseline in CD4+ cell count, and the CD4:CD8 ratio at 24 weeks will be measured. Additionally, acceptability, comfort, suitability, utility, adequacy, quality, perceived benefit, and satisfaction with the intervention will be evaluated at the baseline visit and the week 24 visit. These parameters will be collected using a scale from 0 to 5.
- **Safety Population:** consisting of all patients who have received at least one dose of the study treatment. The following aspects of the study will be measured: Incidence and severity of adverse events (clinical and laboratory) and whether they cause treatment interruption until week 24, and the incidence of genotypic resistance mutations in participants with virological failure at week 48 (the rate of resistance (%) detected among patients with virological failure will be calculated, as well as the incidence of each type of mutation [percentage of patients presenting each type of mutation]).

15.3. Safety and Adherence Analysis

The safety analysis will consist of the description of AEs, abnormal laboratory results (hematology and biochemistry), abnormalities recorded in physical examinations, including altered vital sign values, the incidence of AIDS-related events, manifestations of immune reconstitution inflammatory syndrome, and the relationship of these events with the study treatment. Furthermore, the percentage of patients in whom treatment was discontinued due to toxicity will be calculated. The safety analysis will also include the analysis of deaths occurring during the study, presenting the number and percentage of patients who died and the reason for death. Additionally, an analysis of AEs resulting in the patient's death will be carried out as part of the SAE analysis. A global descriptive analysis will be performed on the number and percentage of patients experiencing any AE, at least one SAE, treatment-related AEs, SAEs resulting in death, and patients who prematurely discontinued treatment due to an AE. Adherence analysis during the treatment period will be performed descriptively by counting returned medication in relation to dispensed medication and using the SMAQ questionnaire. SPSS software will be used for the analysis.

16. Quality Control and Assurance

16.1. Site Procedures

The investigator agrees to conduct the clinical trial in accordance with this protocol, local regulations, international GCP, and the ethical principles originating in the Declaration of Helsinki. The Investigator agrees to complete the e-CRFs according to the sponsor's requirements in a timely, accurate, and legible manner. The site's standard operating procedures will be respected for all clinical and analytical activities relevant to trial quality. Participant compliance will be monitored throughout the trial. The investigator will sign and date any analysis results (e.g., laboratory) to verify that the results have been reviewed. The Investigator may appoint other sub-investigators to collaborate in the trial. However, the investigator maintains responsibility for the trial and will supervise the sub-investigators. Written IEC approval will be obtained before participating in the trial. The investigator will ensure that all research personnel are appropriately trained in GCP, local regulations, the protocol, the drug package insert, and all trial procedures and requirements.

16.2. Monitoring

The Investigator is responsible for the validity of all data collected at the clinical site and must accept the various monitoring procedures employed by the sponsor. The purpose of monitoring is to verify that the rights and well-being of human participants are protected; that trial data are accurate, complete, and verifiable with source data; and that the trial is conducted in accordance with the protocol, international GCP, ethical principles originating in the Declaration of Helsinki, and applicable regulatory requirements. Monitors assigned by the sponsor will conduct periodic visits before, during, and after the trial to oversee various aspects of the trial and ensure its proper conduct in accordance with ICH GCP. Visits will normally be conducted at a predetermined interval, but this may vary during the trial. The Investigator and site staff will allow the trial monitor and authorized representatives of the sponsor to (1) inspect all e-CRFs, informed consent documents, and corresponding source documents (e.g., original medical records), participant records, laboratory data, site SOPs, training records, facilities, and other trial-related systems/processes, and (2) access clinical supplies and storage areas. The investigator and site staff must also (1) agree to assist in monitoring activities if requested and (2) provide adequate time and space for monitoring visits. The monitor will consult with the investigator regarding any missing, confusing, spurious, or ambiguous data. All queries must 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 the confirming signature of the investigator or designee.

16.3. Audit

To comply with international GCP and regulatory agency guidelines, it may be necessary for Quality Assurance personnel authorized by the sponsor and/or authorized personnel from an external regulatory agency to conduct an audit or

inspection of the research site. The purpose of an audit is to evaluate data quality in terms of accuracy, adequacy, and consistency, and to ensure that studies comply with guidelines. Having top-quality study data is an essential aspect of drug development. The investigator and site staff will be given sufficient advance notice to prepare for such visits, which normally last between one and two days and may be conducted at any stage of the trial. The audit will include a review of all trial-related documentation that each site must maintain according to GCP; the storage, dispensing, and return of medications; all trial-related supplies; and trial source documents to ensure the adequacy and accuracy of the information recorded, including verification of any AEs recorded. Auditors or inspectors may also review site SOPs, training records, site facilities, and other trial-related systems/processes. Should the site be notified of a regulatory inspection, the sponsor will assist with preparation. It is essential to notify the sponsor of the inspection as soon as possible.

17. Annual Report to the AEMPS

The objective of the annual report is to facilitate the monitoring tasks of the trial as contemplated in section 4.10 of the ICH Good Clinical Practice guidelines. It must be submitted annually from the start date of the trial in Spain until the trial end date. Data regarding the number of trial participants will be cumulative, and annual data referring to serious breaches, withdrawals and dropouts, and corrective measures adopted will be presented.

18. Suspension or Temporary Interruption of the Trial

If circumstances arise that could jeopardize the safety of the subjects, the sponsor and the investigator shall adopt appropriate urgent measures to protect the subjects from any immediate risk. The sponsor shall inform both the AEMPS and the IECC [CEIm] as soon as possible of such circumstances and the measures adopted to minimize risks and inconveniences for the participants. In said communication, it is necessary to indicate the date on which the interruption was carried out (in the event that it involves a partial or total interruption of the trial), the justification for adopting said measure, the effect thereof (interruption of recruitment, interruption of treatment, complete interruption of the trial, number of patients affected, etc.), and a report on the current status of the trial, at least in Spain. If the trial ends as a result of the reason that led to a temporary suspension, the corresponding notification of completion of a clinical trial must be made.

19. Ethical Aspects

19.1. Basic Principles

This research will be carried out in accordance with international GCP, the ethical principles originating in the Declaration of Helsinki, and applicable regulatory requirements.

19.2. Review by the Independent Ethics Committee (IEC)

The protocol and the necessary documents related to the trial will be reviewed by the respective center IECs. The trial will not begin until the IEC has approved the protocol, the informed consent, any written information to be provided to the participant or any modification thereof, in addition to any other document related to the trial required for review. The IEC shall be constituted and function in accordance with international GCP and the ethical principles originating in the Declaration of Helsinki. The investigator will maintain an accurate and complete record of all submissions and responses from the IEC. The sponsor will send periodic reports to the IEC on the conduct of the clinical trial. The sponsor will notify the Ethics Committee of the completion of the study.

19.3. Regulatory Authorities

Regulatory Authorities will receive the protocol, amendments, reports on SAEs, and the Integrated Clinical Trial Report in accordance with national regulations. As required by legislation, written approval from the Regulatory Authorities will be obtained prior to the start of the trial.

19.4. Legislation / Declaration of Helsinki / ICH / Good Clinical Practices T

he present clinical trial will be conducted in accordance with the protocol, the principles established in the current revised version of the Declaration of Helsinki (Brazil, October 2013), and in accordance with applicable regulatory requirements, in particular the ICH tripartite harmonized guidelines for good clinical practice 1996 and Royal Decree 1090/2015 on clinical trials, which regulates clinical trials with medicinal products in Spain, and which incorporates the specific provisions for the application in Spain of Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on the application of good clinical practices in the conduct of clinical trials of medicinal products for human use. By signing the protocol, the investigator consents to adhere to the instructions and procedures described therein and, in this way, to follow the principles of good clinical practices that they imply. In compliance with Royal Decree 1090/2015, the sponsor will submit the relevant documentation to the IECC. The study will not begin until approval from the IECC and the AEMPS has been obtained. Any amendment that changes the benefit-risk ratio for the patient must be, once signed by the sponsor, submitted to the evaluation of the IECC and the AEMPS for approval (see protocol section). The study investigators will also be informed and will provide their written approval of the same. Informed consent for participation in the study will be freely granted prior to the performance of any study-specific procedure. The study personnel involved in the conduct of this trial will be sufficiently qualified by education, training, and experience to carry out the assigned tasks. This trial will not utilize the services of personnel who have been sanctioned/suspended for scientific fraud or clinical malpractice.

19.5. Patient Information and Informed Consent

Written informed consent will be obtained from all participants (or a legally acceptable representative) before any trial-related procedure is carried out. Investigators may discuss trial availability and entry into the trial with a potential participant without first obtaining consent. However, informed consent must be obtained and documented prior to initiating any procedures performed for the sole purpose of determining eligibility for the research. Investigators have the ethical and legal responsibility to ensure that each participant considered for inclusion in this trial receives a full explanation of the protocol and the potential hazards of the study drug. Participants must be informed that their participation is voluntary. The investigator or their representative will explain the nature of the trial to the participant or their legally authorized representative and will answer all questions related to the trial. This must be documented in a written informed consent form that must be approved by the same IEC responsible for the approval of this protocol. Each informed consent form will include the elements required by international GCP and must adhere to the ethical principles originating in the Declaration of Helsinki. Once the investigators (or their qualified representatives) have provided the participant with the appropriate essential information and it is considered that the participant understands the implications of their participation, the written informed consent form approved by the IEC will be signed and dated by both. The written informed consent form approved by the IEC will be signed and dated by the participant and the person obtaining the consent (investigators or designees). Ongoing participants must re-consent to the most recent version of the IC(s) during their participation in the trial. The original signed informed consent form will be kept with the trial records and a copy of the signed informed consent form will be provided to the participant or their legally authorized representative. Another copy of the signed informed consent form and a source document identifying the trial and recording the dates of participation will be included in the participant's medical history. The monitor will inspect the original consent forms of all participants. In the event that any new version of the patient information sheet and informed consent is generated during the course of the study, it must be approved by the IECC and the AEMPS. Following this, the investigator must fully inform the patient and request that they grant their informed consent again.

20. Data Management and Archiving of Records

20.1. Confidentiality

Information disseminated and obtained during the present study will be considered confidential and must be treated as such at all times. Patients included in the study will be identified only by a code, such that no personal identifying data of the patient will be collected in the sponsor's study database. In this way, the sponsor will work with pseudonymized data. The dissociation procedure will be

carried out by the investigators participating in the study, who will create a list linking the personal data of the patients with the code assigned by the sponsor that will identify the patient during the study. This list will be kept at the base center at all times, being maintained in the investigator's file. All material, information (oral or written), and unpublished documentation provided to the investigators, including this protocol and the e-CRFs, must be considered the property of the sponsor. Study data and/or material may not be disclosed, in part or in whole, to any unauthorized person without the prior formal written consent of the coordinating investigator. The content of the e-CRFs, as well as the documents generated during the study and the electronic database, will be protected from unauthorized use by persons outside the research and, therefore, will be considered strictly confidential and will not be disclosed to third parties except those specified in the previous section. Only those data from the medical history that are related to the study will be subject to verification. This verification will be done as far as possible in the presence of the principal investigator/co-investigators, and the confidentiality of all personal data of the subjects participating in the clinical trial will be maintained at all times, as provided for in the applicable regulations according to Regulation (EU) 2016/679, of 27 April, General Data Protection Regulation, and its implementing personal data regulations both at national and European levels. The information obtained will be stored in a database, on computer media, registered with the Spanish Data Protection Agency, according to current legislation. The coordinating investigator will allow direct access to source data and documents for monitoring, auditing, review by the IECC, as well as inspection of the study by health authorities. Said access will be restricted to the sponsor, monitor, study healthcare personnel and their collaborating team, AEMPS, competent health authorities of the autonomous communities, IECC, and sponsor or personnel authorized by the sponsor, when they require it to verify the study data and procedures, but always maintaining the confidentiality thereof in accordance with current legislation. The sponsor is obliged to publish the results of the study in scientific journals, guaranteeing at all times the anonymity of the participating study subjects.

20.2. Data Collection in the Case Report Form (CRF)

Data collection in the Case Report Form (CRF) will comply with data protection legislation. REGULATION (EU) No. 536/2014 requires that trial subjects' data be treated in accordance with Union legislation on data protection. In Spain, Organic Law 3/2018, of 5 December, on the Protection of Personal Data and guarantee of digital rights is in force, complementary to Regulation (EU) 2016/679 of the European Parliament and of the Council, of 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC. This legislation requires the application of high-level security measures in the handling of health data, such that the distribution of media is carried out by encrypting said data or by using another mechanism that guarantees that said information is not accessible or manipulated during transport. Data related to health are considered by the LOPD to be specially protected data, which merit a stricter protection regime, this being a

broad concept that includes information concerning the past, present, and future health, physical or mental, of an individual, including the percentage of disability and their genetic information. For this reason, the case report form must only include a code that does not allow identification of the subject. Furthermore, it may not collect identifying data of the subjects participating in the study: medical record number or similar assigned by the Administration, name, surnames, subject's initials, postal address or email address, telephone number, tax identification number, fingerprint, DNA, a photograph, or social security number.

20.3. Study Archive

For the purpose of the study, a file will be generated with all study documentation that will be kept by the investigator at their center (investigator's file) and another kept by the sponsor (sponsor's file). The content of said files will comply with the requirements for study documentation in accordance with the requirements of ICH-Good Clinical Practices and current regulations. Study documentation will be preserved for the time required by current legislation.

21. Publication of Results

Results will be presented first at national and international congresses, giving priority to oral presentation. Subsequently, an article will be prepared for submission to international scientific journals for publication (first-quartile journals). Simultaneously, parallel dissemination will be carried out through information channels (social networks, newspapers, radio or television interviews). Manuscripts generated with the data from this study must follow the good publication practices indicated by the International Committee of Medical Journal Editors (ICMJE) and Good Publication Practice 2 (GPP2). Regarding authorship and results publication policy, the rules established by the principal investigator will be observed. The anonymity of the patients participating in the study will be guaranteed at all times. Before submitting the work for publication, a copy will be sent to the sponsor as reflected in the contract with the sponsor, to the promoter, and to each of the authors so that they may make the modifications they deem appropriate. If there is no response within the maximum time set by the person responsible for the protocol, it will be considered that there is agreement with the content of the work.

22. Protocol

22.1. Protocol Amendments

Any changes to the protocol will be made through an amendment to the same, if applicable. Any changes affecting the safety or well-being of the participants will be submitted to the IEC and Regulatory Authorities prior to their implementation. The investigator, the IEC, and the sponsor must agree on all amendments. No modification will be implemented until it is approved by the authorities and/or the IEC and signed by all required parties. Exceptions to this occur when the investigator considers that participant safety is compromised. Protocol amendments detailing minor administrative changes must be submitted by the investigator, either for notification or approval, as appropriate.

22.2. Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol, GCP, or the monitoring plan requirements. Non-compliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, the site must develop corrective actions, which shall be implemented promptly. It is the responsibility of the site to use continuous surveillance to identify and report deviations. All deviations must be addressed in the study source documents and reported to the sponsor/designee. Protocol deviations must be sent to the local EC according to its guidelines. The PI/site study staff is responsible for knowing and complying with their IEC's requirements. When a protocol deviation is required to circumvent immediate risks to patients, the investigator will contact the sponsor, if circumstances allow, to discuss the measures planned to be taken. The IECCs [CEIm] and health authorities will be informed regarding protocol deviations detected during the conduct of the study.

22.3. Investigator Acceptance

Both the initial protocol and all amendments generated must be accepted by all principal investigators participating in the clinical trial. To this end, investigators will sign a document of acceptance of the protocol and its potential subsequent amendments.

23. Sponsor, Financial Aspects, Insurance, and Indemnity

The project has been funded with a financial contribution from the Gilead Sciences ISR call with project number: IN-ES-380-6205. The trial sponsor is the Fundación SEIMC-GESIDA. All financial aspects related to the clinical trial will be reflected in a contract between the promoter and the sponsor. The financial memorandum of the study will be made available to the corresponding IECC for evaluation. As required by current legislation, and in particular Royal Decree 1090/2015, the sponsor has taken out an insurance policy with the insurance company HDI Global SE, Branch in Spain, located at c/ Luchana, 23, 5a, 28010 Madrid, policy number 08058154-30015. This policy covers the liabilities of the sponsor/principal investigator, their collaborators, and the centers where the clinical trial is conducted, against

potential damages and losses affecting the patient's health derived from this research, strictly conducted in accordance with both the scientific protocol and the applicable law in Spain and professional standards, during the conduct of the study and in the year following its completion, unless proven otherwise. The insurance does not exempt investigators from the obligation to maintain their own civil liability insurance, as required by applicable law.

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Appendices

Appendix 1: Project Vehicles

Figure 1. Mobile Screening Unit.

Figure 2: DAS Service Vehicle.

Appendix 2: Serious Adverse Events Notification Form

SERIOUS ADVERSE EVENT REPORT FORM
SEIMC-GESIDA Foundation

Principal Investigator: **Site:** **Phone:** **Country:**	**PROTOCOL CODE** (sponsor)..... **EUDRACT N°/ Protocol N°** AEMPS.....	☐ Initial Report ☐ Follow up Report
NOTIFICATION N° (to be completed by sponsor):		

I. INFORMATION ABOUT THE ADVERSE EVENT

PATIENT CODE:	**DATE OF BIRTH** (dd/mm/yyyy):	**AGE** (Years):	☐ **MALE** ☐ **FEMALE**	**WEIGHT** (Kg):	**HEIGHT** (cm):	**SAE START DATE** (dd/mm/yyyy):	**SAE START TIME** (hh:mm):

SERIOUS ADVERSE EVENT:	Detail the symptoms if there is no diagnosis:	**SERIOUS CRITERIA** ☐ PATIENT DIED (EXITUS) ☐ LIFE THREATENING ☐ HOSPITALIZATION ☐ PROLONGED HOSPITALIZATION ☐ PERSISTENCE OR SIGNIFICANT DISABILITY/INCAPACITY ☐ CLINICALLY RELEVANT EVENT ☐ PREGNANCY **SEVERITY** ☐ MILD ☐ MODERATE ☐ SEVERE ☐ LIFE THREATENING **¿HAS THE SERIOUS ADVERSE EVENT ENDED?** ☐ YES ☐ NO **END DATE**: (DD/MM/YYYY) _____ **SAE OUTCOME:** ☐ PERSISTENCE OF SAE ☐ RESOLVED WITHOUT SEQUELAE ☐ RESOLVED WITH SEQUELAE ☐ UNKNOWN ☐ EXITUS
DATE OF KNOWLEDGE OF SERIOUS ADVERSE EVENT (DD/MM/YYYY):		
DESCRIPTION OF THE SERIOUS ADVERSE EVENT (Including relevant exploration, laboratory results, course of the event, etc)		
HAS A LACK OF QUALITY BEEN DETECTED IN THE SUSPECTED PRODUCT? ☐ YES ☐ NO		
IS IT A SUSPECTED TRANSMISSION OF AN INFECTIOUS AGENT THROUGH A MEDICAL PRODUCT?: ☐ YES ☐ NO		
WAS THE SUBJECT WITHDRAWN FROM THE STUDY DUE TO THE SAE? ☐ YES ☐ NO		

II. SUSPECT DRUG INFORMATION

SUSPECT DRUG:	**DAILY DOSE** (Include units)	**ROUTE**	**INDICATION FOR USE:**	**START DATE** (dd/mm/yyyy):

ACTION TAKEN WITH SUSPECT DRUG:
☐ None ☐ Temporary interruption ☐ Permanent interruption ☐ Dose increase ☐ Dose decrease

INTERRUPTION DATE (dd/mm/yyyy):	**REINTRODUCTION DATE** (dd/mm/yyyy):

DID THE REACTION DIMINISH WHEN THE MEDICATION WAS SUSPENDED?	DID THE REACTION DIMINISH WHEN THE MEDICATION DOSE WAS DECREASED?	DID THE REACTION RE-APPEAR WHEN THE MEDICATION WAS RE-INTRUDUCED?
☐ YES ☐ NO ☐ NOT APPLY	☐ YES ☐ NO ☐ NOT APPLY	☐ YES ☐ NO ☐ NOT APPLY

III. CONCOMITNANT MEDICATIONS AND MEDICAL HISTORY

CONCOMITANT MEDICATION (Mark with an asterisk the suspect drug (s))	DAILY DOSE (Include units)	ROUTE	START DATE (dd/mm/yyyy)	END DATE (dd/mm/yyyy)	SAE TREATMENT (mark only if medication has been used to treat the SAE)	INDICATION (complete when medication has not been used to treat the SAE)
					☐	
					☐	
					☐	
					☐	
	RELEVANT INFORMATION OF THE MEDICAL HISTORY (ej. Diagnostics, allergies, pregnancies, etc.)					

IV. RELATIONSHIP OF THE CAUSALITY OF THIS SERIOUS ADVERSE EVENT TO THE SUSPECTED DRUG/S

INVESTIGATOR'S JUDGMENT:	SPONSOR'S JUDGMENT:
☐ Related ☐ Not related	☐ Related ☐ Not related

V. INFORMATION OF THE SPONSOR AND INVESTIGATOR

SPONSOR ADDRESS Fundación SEIMC-GESIDA C/ Agustín de Betancourt nº 13 - entreplanta 28003 Madrid	NAME AND PHONE OF THE INVESTIGATOR WHO REPORT THE SAE:
REPORT DATE (dd/mm/yyyy):	COMPLEMENTARY REPORT ATTACHED ☐ YES ☐ NO

INVESTIGATOR WHO COMPLETE THE REPORT:

Name: _____

Signature: _____

Date: _____

PERSONAL OF THE SPONSOR WHO RECEIVE THE REPORT:

Name: _____

Signature: _____

Reception date at SEIMC-GESIDA Foundation (DD/MM/YYYY):

Appendix 3: Pregnancy Notification Form

CONFIDENTIAL

Protocol Identifier	Subject Identifier	Centre Number
☐☐☐☐☐☐☐☐☐☐	☐☐☐☐☐☐	☐☐☐☐☐☐

PREGNANCY NOTIFICATION FORM

This form should be completed according to the protocol reporting requirements.
Note: Most protocols do not require collection of subject's partner pregnancy.
Complete this form for each subject or subject's partner who becomes pregnant during the study period. Send a copy of the form to FSG (Email or fax number +34 915542283).

Who is this form being completed for, ✓*one:* ☐ Subject

☐ Subject's partner

MOTHER'S RELEVANT MEDICAL/FAMILY HISTORY

Mother's year of birth ☐☐☐☐ Year

Date of last menstrual period ☐☐ Day ☐☐☐ Month ☐☐ Year

Estimated date of delivery ☐☐ Day ☐☐☐ Month ☐☐ Year

Was the mother using a method of contraception? ☐ Yes ☐ No

If Yes, specify: _____

Type of conception, ✓*one:* ☐ Normal (includes use of fertility drugs)
☐ IVF (in vitro fertilisation)

Relevant laboratory tests and procedures (e.g., ultrasound, amniocentesis and chorionic villi sampling, including dates of tests and procedures).

_____

_____

Number of previous pregnancies ☐☐ Pre-term ☐☐ Full-term

If applicable, record the number in the appropriate categories below:

☐☐ Normal births
☐☐ Stillbirths
☐☐ Children born with defects
☐☐ Spontaneous abortion
☐☐ Elective abortion
☐☐ Other

Record details of children born with defects: _____

Are there any additional factors that may have an impact on the outcome of this pregnancy? ☐ Yes ☐ No

If Yes, specify: _____

Protocol Identifier	Subject Identifier	Centre Number

PREGNANCY NOTIFICATION FORM (Continued)

FATHER'S RELEVANT MEDICAL/FAMILY HISTORY

Only recorded if required by the protocol and Informed Consent of the father has been obtained.

(Include habitual exposures such as alcohol/substance abuse, chronic illnesses, familial birth defects/genetic/ chromosomal disorders and medication use)

_____

_____

DRUG EXPOSURES

In the following table, list all medications (including study medications) the subject received during the study period (e.g. prescription, OTC, vaccines, recreational, alcohol, etc.). Enter the investigational product details on the first line (if the investigational product is blinded, enter 'Investigational Product' on this line). If there are extensive concomitant medications, attach a copy of the Concomitant Medications CRF page.

Drug Name *(Trade Name preferred)*	**Route of Admin. or For-mulation**	**Total Daily Dose**	**Units**	**Started Pre-Study** Y=Yes N=No	**Start Date** Day Month Year	**Stop Date** Day Month Year	**Ongoing Med-ication** Y=Yes N=No	**Reason for Medication**

Was the subject withdrawn from the study as a result of this pregnancy? ☐ Yes ☐ No

REPORTING INVESTIGATOR INFORMATION *(Forward to a more appropriate physician if needed)*

Name _____ Title __ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code _____

Telephone No _____

Fax No _____

Investigator's signature _____ Date ☐☐ Day ☐☐☐ Month ☐☐ Year
(confirming that the data on these pages are accurate and complete)

Investigator's name (print) _____

Appendix 4: Pregnancy Follow-up Form

Protocol Identifier	Subject Identifier	Centre Number

PREGNANCY FOLLOW-UP FORM - CURRENT PREGNANCY INFORMATION

One form should be completed per foetus (e.g., if a subject is carrying twins a form should be completed for each twin).

Who is this form being completed for, ✓ *one:* ☐ Subject ☐ Subject's partner

PREGNANCY STATUS

While pregnancy itself is not an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. A spontaneous abortion is always considered to be an SAE and will be reported as described in the protocol. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the Investigator will be reported to FSG per the protocol. Whilst the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Early termination, ✓ *if applicable:*

☐ Stillbirth
☐ Foetal death
☐ Method used for delivery, *specify* _____

☐ Spontaneous abortion
☐ Elective abortion
☐ Other, *specify* _____

InForm studies:

- *If a female subject is pregnant and the outcomes/associated events fulfill the criteria of an SAE, complete the information in the eCRF SAE form and on this paper Pregnancy Follow-up form.*
- *If male subject's partner is pregnant and the outcomes/associated events fulfill the criteria of an SAE, then complete the information in the paper SAE form and send together with this paper Pregnancy Follow-up form.*

Paper studies: *If any of the outcomes/associated events fulfil the criteria of an SAE, complete the SAE section in the CRF.*

FOETAL/NEONATAL STATUS

☐ Normal
☐ Birth defect (i.e., structural/chromosomal disorder) *Complete Serious Adverse Event pages*
☐ Other disorder (e.g., non-structural, premature birth, intrauterine death/stillbirth)

If birth defects are diagnosed, is the origin of the defect known? ☐ Yes ☐ No

If Yes, specify _____

INFANT INFORMATION

Date of birth/miscarriage/termination ☐☐ ☐☐☐ ☐☐ (Day Month Year)

Gestational weeks at birth/miscarriage/termination ☐☐ Weeks

Infant's sex ☐ Male ☐ Female ☐ Unknown

Length ☐☐.☐ cm Weight ☐☐☐☐.☐☐ g

Apgar score (0 - 10) ☐☐ First assessment ☐☐ Second assessment

CONFIDENTIAL

Protocol Identifier	Subject Identifier	Centre Number

PREGNANCY FOLLOW-UP FORM - CURRENT INFORMATION (Continued)

ADDITIONAL DETAILS *(Provide additional details on current labour/delivery/discharge notes etc.)*

_____

_____

_____

_____

DRUG EXPOSURES DURING PREGNANCY

Complete drug section for all drugs (including OTC/vaccines) taken by the mother during pregnancy. Do not include drugs that have already been included on the Pregnancy Notification Form.

Drug Name *(Trade Name preferred)*	**Route of Admin. or For-mulation**	**Total Daily Dose**	**Units**	**Started Pre-Study** Y=Yes N=No	**Start Date** Day Month Year	**Stop Date** Day Month Year	**Ongoing Med-ication** Y=Yes N=No	**Reason for Medication**

REPORTING INVESTIGATOR INFORMATION *(Forward to a more appropriate physician if needed)*

Name _____Title ___ Speciality _____

Address _____

City or State/Province _____

Country _____

Post or Zip Code_____

Telephone No _____

Fax No _____

Investigator's signature _____ Date ☐☐ ☐☐☐ ☐☐
(confirming that the data on these pages are accurate and complete) Day Month Year

Investigator's name (print) _____

Appendix 5: a) Hospital Anxiety and Depression Scale (HADS)

Original version by Zigmond and Snaith, 1983

This questionnaire has been designed to help us understand how you feel. Read each sentence and mark the answer that best describes how you felt during the past week. Do not think too much about your answers. Most likely, if you answer quickly, your responses will better reflect how you really felt.

1. I feel tense or 'wound up'.

☐ Most of the time

☐ A lot of the time

☐ From time to time

☐ Not at all

2. I still enjoy the things I used to enjoy.

☐ Definitely as much

☐ Not quite so much

☐ Only a little

☐ Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen.

☐ Very definitely and quite badly

☐ Yes, but not too badly

☐ A little, but it doesn't worry me

☐ Not at all

4. I can laugh and see the funny side of things.

☐ As much as I always could

☐ Not quite so much now

☐ Definitely not so much now

☐ Not at all

5. Worrying thoughts go through my mind.

☐	Most of the time
☐	A lot of the time
☐	From time to time, but not too often
☐	Only occasionally

a) WHOQOL-BREF QUALITY OF LIFE SCALE

Before starting the test, we would like you to answer some general questions about yourself: please circle the correct answer or write in the blank space.

Sex: Male / Female

When were you born? Day / Month / Year

What is your level of education? None / Primary / Secondary / University

What is your marital status?		
Single	Separated	Married
Divorced	In a partnership	Widowed

Are you currently ill? Yes / No

If you have a health problem, what do you think it is? Disease/Problem:

_____

Instructions: This questionnaire is intended to find out your opinion about your quality of life, your health, and other areas of your life. **Please answer all questions**. If you are not sure what answer to give to a question, choose the one that seems most appropriate. Sometimes, this may be the first answer that comes to mind.

Please keep in mind your way of living, expectations, pleasures, and concerns. We ask you to think about your life during the last two weeks. For example, thinking about **the last two weeks**, you might ask yourself**:**

	Not at all	A little	Moderate	Mostly	Completely
Do you get the support you need from others?	1	2	3	4	5

Circle the number that best defines how much support you received from others in the last two weeks. If you think you received quite a lot of support from others, you should circle number 4, as follows:

		Not at all	A little	Moderate	Mostly	Completely
	Do you get the support you need from others?	1	2	3	(4)	5

Remember that any number is valid; the important thing is that it represents your opinion.

Please read the question, assess your feelings, and circle the number on the scale that best represents your answer choice.

		Very poor	Poor	Neither poor nor good	Fairly good	Very good
1	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	A little dissatisfied	Neither satisfied nor dissatisfied	Fairly satisfied	Very satisfied
2	How satisfied are you with your health?	1	2	3	4	5

The following questions refer to the extent to which you have experienced certain events in the last two weeks.

		Not at all	A little	Moderate	Mostly	Extremely
3	To what extent do you think (physical) pain prevents you from doing what you need to do?	1	2	3	4	5
4	To what extent do you need medical treatment to function in your daily life?	1	2	3	4	5
5	How much do you enjoy life?	1	2	3	4	5
6	To what extent do you feel that your life has meaning?	1	2	3	4	5
7	What is your ability to concentrate?	1	2	3	4	5

		Not at all	A little	Moderate	Mostly	Extremely
8	How safe do you feel in your daily life?	1	2	3	4	5
9	How healthy is the physical environment around you?	1	2	3	4	5

The following questions refer to whether you experienced or were able to do certain things in the last two weeks, and to what extent.

		Not at all	A little	Moderately	Mostly	Completely
10	Do you have enough energy for daily life?	1	2	3	4	5
11	Are you able to accept your physical appearance?	1	2	3	4	5
12	Do you have enough money to meet your needs?	1	2	3	4	5
13	Do you have the information you need for your daily life?	1	2	3	4	5
14	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5
15	Are you able to move from one place to another?	1	2	3	4	5

CONTINUED ON THE NEXT PAGE

The following questions refer to how satisfied you have felt and to what extent, regarding various aspects of your life in the last two weeks.

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16	How satisfied are you with your sleep?	1	2	3	4	5
17	How satisfied are you with your	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
	ability to perform your daily life activities?					
18	How satisfied are you with your capacity for work?	1	2	3	4	5
19	How satisfied are you with yourself?	1	2	3	4	5
20	How satisfied are you with your personal relationships?	1	2	3	4	5
21	How satisfied are you with your sex life?	1	2	3	4	5
22	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23	How satisfied are you with the conditions of the place where you live?	1	2	3	4	5
24	How satisfied are you with your access to health services?	1	2	3	4	5
25	How satisfied are you with the transport services in your area?	1	2	3	4	5

CONTINUED ON THE NEXT PAGE

The following question refers to the frequency with which you have felt or experienced certain feelings in the last two weeks.

Did someone help you fill out the questionnaire? _____

How long did it take you to answer it? _____

Would you like to make any comments about the questionnaire?

_____

Appendix 6: Evaluation of acceptability, comfort, suitability, utility, adequacy, quality, perceived benefit, and satisfaction with the intervention

Would you recommend this service to someone you know?

1. Very satisfied
2. Quite satisfied
3. Fair/Average
4. Quite dissatisfied
5. Very dissatisfied

Has it helped you to access the HIV clinic?

1. Very satisfied
2. Quite satisfied
3. Fair/Average
4. Quite dissatisfied
5. Very dissatisfied

Has it helped you to continue with the follow-up of your disease?

1. Very satisfied
2. Quite satisfied
3. Fair/Average
4. Quite dissatisfied
5. Very dissatisfied

Regarding having a person accompany you to the hospital, what was your level of satisfaction?

1. Very satisfied
2. Quite satisfied
3. Fair/Average
4. Quite dissatisfied
5. Very dissatisfied

Regarding having a person accompany you during the HIV consultation, what was your level of satisfaction?

1. Very satisfied
2. Quite satisfied

3. Fair/Average
4. Quite dissatisfied
5. Very dissatisfied

The service helped you collect medication at the hospital. What was your level of satisfaction?

1. Very satisfied
2. Quite satisfied
3. Fair/Average
4. Quite dissatisfied
5. Very dissatisfied

HIV treatment was started immediately. What was your level of satisfaction?

1. Very satisfied
2. Quite satisfied
3. Fair/Average
4. Quite dissatisfied
5. Very dissatisfied

The quality of the service is good. What was your level of satisfaction?

1. Very satisfied
2. Quite satisfied
3. Fair/Average
4. Quite dissatisfied
5. Very dissatisfied

Your overall level of satisfaction with the MSU [UMC] was:

1. Very satisfied
2. Quite satisfied
3. Fair/Average
4. Quite dissatisfied
5. Very dissatisfied

How would you rate the treatment received from the research team?

1. Very satisfied

2. Quite satisfied
3. Fair/Average
4. Quite dissatisfied
5. Very dissatisfied

Did you find it comfortable?

1. Yes
2. No
3. DK/NA (Don't know / No answer)

Do you believe that without this service you would have access to treatment?

1. Yes
2. No
3. DK/NA

Do you believe that starting treatment as soon as possible has helped you follow up better?

1. Yes
2. No
3. DK/NA

The healthcare team that attended to you was competent.

1. Yes
2. No
3. DK/NA

The healthcare team clarified all your doubts.

1. Yes
2. No
3. DK/NA

Did you find the way you were attended to useful (being taken and seen at the hospital)?

1. Yes
2. No
3. DK/NA

Did you find the way they explained topics related to HIV infection or the study procedure useful?

1. Yes
2. No
3. DK/NA

Did you find the treatment you received from the healthcare staff appropriate?

1. Yes
2. No
3. DK/NA

The service helped you collect medication at the hospital. Did you find it useful?

1. Yes
2. No
3. DK/NA

The service accompanied you to the hospital. Did you find it useful?

1. Yes
2. No
3. DK/NA

Comment why: _____

The service helped you with the follow-up of your HIV disease. Did you find it useful?

1. Yes
2. No
3. DK/NA

Comment why: _____

Has participating in this study facilitated your access to receiving care from a doctor?

1. Yes
2. No
3. DK/NA

Has participating in this study facilitated your ability to start or restart your HIV medication?

1. Yes
2. No
3. DK/NA

Has participating in this study facilitated continuing with your follow-up at consultations?

1. Yes
2. No
3. DK/NA

Would you prefer to go to the hospital by other means?

1. Yes
2. No
3. DK/NA

Have you been adequately informed about the circuit you will follow in the coming months?

1. Yes
2. No
3. DK/NA

Regarding the HIV infection, have you been adequately informed by the team?

1. Yes
2. No
3. DK/NA

Rate your experience in this study from 0 to 10. 0–10 (0 Very poor, 10 Excellent)

Appendix 7: SMAQ Adherence Questionnaire

1. Do you ever forget to take your medication?

☐ Yes

☐ No

2. Are you careless at times about taking your medication?

☐ Yes

☐ No

3. When you feel better, do you sometimes stop taking your medication?

☐ Yes

☐ No

4. If you ever feel worse after taking the medication, do you stop taking it?

☐ Yes

☐ No

5. In the last week, how many times did you miss a dose?

☐ A: none

☐ B: 1–2

☐ C: 3–5

☐ D: more than 5

Since when: _____

Interpretation

A patient is considered non-adherent if any of the following responses are given:
1: Yes, 2: No, 3: Yes, 4: Yes, 5: C or D (more than two missed days).

The questionnaire is dichotomous: any response indicating non-adherence classifies the patient as non-adherent.

Question 5 may also be used semi-quantitatively:
A: 95–100%

B: 85–94%
C: 65–84%
D: <65%

References:

Expert group of the Secretariat of the National Plan on AIDS (SPNS), AIDS Study Group (GESIDA), and Spanish Society of Hospital Pharmacy (SEFH). Consensus document to improve adherence to pharmacotherapy in patients with human immunodeficiency virus infection receiving antiretroviral treatment (February 2020 update). Knobel H, Alonso J, Casado JL, et al. Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA Study. AIDS 2002; 16 (4):605-13.