PerimenopausE and older Adults with HIV - tReatment outcomes and Lived experience



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The undersigned confirm that the following protocol has been agreed that the Chief Investigator intends to conduct the study in compliance with the approved protocol and will adhere to the national guidelines for the conduct of clinical research.

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

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

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1. List of Abbreviations

Drug Class Name	
INSTI	Integrase strand transfer inhibitor
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI	Nonnucleoside reverse transcriptase inhibitor
PI	Protease inhibitor
General Terminology	
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
BHIVA	British HIV Association
BMI	Body Mass Index
B/F/TAF	Bictegravir/emtricitabine/tenofovir alafenamide
CRF	Case Report Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FRAIL Scale	Fatigue, Resistance, Ambulation, Illnesses, Loss of weight Scale
GAD-7	Generalised Anxiety Disorder-7 Questionnaire
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRA	Health Regulatory Authority
HIV	Human Immunodeficiency Virus
HIVTSQ	HIV Treatment Satisfaction Questionnaire
ICF	Informed Consent Form
ISERP	Independent Safety Epidemiology Review Panel
IQR	Inter-Quartile Range
LA	Long-acting
MDT	Multidisciplinary Team
µL	Microlitre
mL	Millilitre
NHS	National Health Service
PIS	Participant Information Sheet
PLWH	People living with HIV
PD	Protocol Deviation
PHQ-9	Patient Health Questionnaire-9
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measures
PROMIS	Patient-Reported Outcomes Measurement Information System
PV	Protocol Violation
QA	Quality Assurance
REDCap	Research Electronic Data Capture
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction

SMG	Study Management Group
SUSAR	Suspected Unexpected Serious Adverse Reaction
VL	Viral Load (HIV-1 RNA)

2. Protocol summary

Title	PerimenopausE and older Adults tReatment outcomes and Lived experience
Study Acronym	PEARL
Rationale	From 2000 to 2016, average life expectancy for people with HIV rose from 58 to 77 years. In many developed countries, over half of people with HIV are now aged 50 years or older, a demographic expected to grow year on year. Evidence on which treatment regimens are optimal in peri/post-menopausal and older adults is limited, despite heightened susceptibility to neuropsychiatric adverse effects and frequent sleep or mood disturbance. Randomised clinical trials (RCTs) have established the safety, efficacy, and tolerability of bictegravir in combination with emtricitabine and tenofovir alafenamide (B/F/TAF). However, populations included in clinical trials often fail to reflect the wider demographics of those who ultimately receive the regimen. For example, in the key RCTs on B/F/TAF only ~10-12% of the clinical trial participants were female and the median age of participants was 31-33 years. There is limited evidence on key patient-reported outcomes such as sleep, mood, quality of life and treatment satisfaction(1, 2). Despite the lack of clinical trial data on B/F/TAF in older people, this regimen is often used in older adults at risk of renal disease or osteoporosis because of its favourable kidney and bone profile. Therefore, there is a need for real-world data on the experiences of B/F/TAF within critical subpopulations such as peri/post-menopausal adults and older people affected by geriatric syndromes. This empirical evidence can be used to guide and improve individualised treatment in HIV care. The findings of this multicentre mixed-methods cohort study will generate evidence on treatment options for women and older adults. Findings will strengthen the evidence base for individualised HIV care, and support the delivery of age- and menopause-responsive services.

Primary objectives	1. Describe detailed patient reported outcomes before and after switch of HIV treatment in adults in the peri/post-menopausal period and/or ≥60 years of age, with a focus on sleep, mood, treatment satisfaction, quality of life and frailty
Secondary objectives	2. Explore lived experiences after switching treatment to B/F/TAF among peri/post-menopausal and older adults 3. Characterise HIV clinicians' perceptions and experiences of the optimal treatment regimens for peri/post-menopausal women and older adults and the clinical factors guiding choice of regimens 4. Describe clinical indications for switching to B/F/TAF or other regimens in peri/post-menopausal and older adults 5. Using routinely collected data, describe long-term HIV treatment outcomes for peri/post-menopausal and older adults on B/F/TAF
Primary outcome measures	Patient-reported outcomes at baseline (pre switch), ~2 and ~6 months post-switch: a) Sleep quality (PROMIS) b) Mood (PHQ-9, GAD-7) c) Quality of life (HIVPROM) d) Treatment satisfaction (HIVTSQ) e) Frailty score (FRAIL scale)
Design	This is a multi-centre, mixed-methods observational study conducted at NHS HIV treatment centres, incorporating both a routinely collected data cohort and a prospective patient-reported outcomes (PROMs) cohort, alongside a nested qualitative element. 1. **PROMs cohort:** a prospective component will recruit 120 individuals switching to B/F/TAF or any other regimens (controls) during routine care; PROMs including sleep, mood, frailty, treatment satisfaction and health-related quality of life, will be captured longitudinally. In-depth qualitative interviews with a subset of participants will explore lived experience of symptoms and treatment effects. 2. **Routine data cohort:** longitudinal routinely collected data will be analysed from 500 adults in the peri/post-menopausal period or aged ≥60 years who are already

	receiving B/F/TAF (outcomes: viral load, weight, bone density where available, renal parameters). 3. **Clinician qualitative study:** Focus groups with HIV clinicians (n = 18-24) will examine desirable therapeutic profile, preferred treatment options, and the decision-making process for peri/post-menopausal adults and those ≥60 years of age.
Population	Approximately 620 adults with HIV who are in the peri/post-menopausal period (≥40 years of age) or ≥60 years of age will be recruited to one of two cohorts: 1. **PROMs prospective cohort:** those who are prospectively switching HIV treatment as part of routine care, either to B/F/TAF or any other regimen (control group, n = 120) 2. **Routine data cohort:** those who have already switched to B/F/TAF prior to study enrolment (n = 500)
Duration	Individual follow-up starts on the date that B/F/TAF is initiated. • Routine data cohort: up to 5 years' follow-up. The follow-up ends earlier if B/F/TAF is discontinued or at study close, whichever occurs first. • PROMs cohort: up to 8 months' follow-up
Statistical methods	Demographic characteristics at the time of switch to B/F/TAF, medical and HIV characteristics will be summarised using descriptive statistics. Data from the routine data cohort will be analysed for durability/tolerability as will the cumulative proportion remaining on B/F/TAF without discontinuation at 12, 24, 36, 48 and 60-months. Reason for discontinuation will be captured. Efficacy will be considered as the proportion with HIV VL <50 copies/mL and the cumulative incidence of virological failure will also be described. In the PROMs cohort, the change in patient-reported outcomes between 0, 2 and 6 months will be analysed. The change in PROMs between the B/F/TAF group and controls will be compared via generalised linear regression adjusted for

	confounders. Frailty in the prospective component will be analysed as change in FRAIL scale score between baseline and 6 months using standard linear regression adjusted for confounding factors. Qualitative data will be analysed by reflexive thematic analysis.
Sample size	Routine data cohort: 500 PROMs cohort: 120

3. Background and rationale

In the global north, the majority of people receiving HIV care are over 50 years old (3-5). This demographic is also growing rapidly in sub-Saharan Africa and by 2040, it is expected to triple, with up to 10 million people over 50 years of age living with HIV. Ageing people face distinct challenges including a disproportionate burden of age-related comorbidities, polypharmacy, drug-drug interactions, and increased vulnerability to neuropsychiatric side effects of HIV medications such as sleep or mood disturbances. Individuals affected by geriatric syndromes (such as frailty), and peri/post-menopausal women are particularly vulnerable to neuropsychiatric side effects of medications, including sleep disturbances. Sleep disturbances have been documented in 61% of perimenopausal women living with HIV on antiretroviral therapy (ART) (6), and in up to 77% of older adults with HIV on ART(7). Additionally, mood disorders, including anxiety and depression, are prevalent, affecting approximately 50% of perimenopausal women with HIV on ART (8) and 15–49% of older adults with HIV on ART (9). Considering that globally 12% of people with HIV over the age of 50 are affected by frailty and 47% are identified as pre-frail (10), and with over half of people with HIV globally being women, there is a need for tailored treatment approaches that address both physiological and psychological considerations in this demographic.

Randomised clinical trials have established the safety, efficacy, and tolerability of B/F/TAF in people living with HIV (11-14). However, populations included in clinical trials often fail to reflect the wider demographics of those who ultimately receive the treatment. For example, in these key studies only ~10-12% of the clinical trial participants were female and the median age of participants was 31-33 years (11-14). Importantly, there is limited evidence on key patient-reported outcomes such as treatment satisfaction, sleep and mood (1, 2). Despite the lack of clinical trial data on B/F/TAF in older people, this regimen is often used in older adults at risk of renal disease or osteoporosis because of its favourable kidney and bone profile.

Emerging evidence suggests that switching to B/F/TAF from other regimens may reduce symptoms such as fatigue and dizziness (15, 16), while potentially enhancing sleep quality (15, 17). Whilst these findings are promising, they necessitate further validation from larger methodologically robust studies that incorporate an appropriate comparator group. Therefore, there is a need for real-world data on the impact of B/F/TAF within critical subpopulations such as older people affected by geriatric syndromes and peri/post-menopausal individuals. The experiences and insights of HIV clinicians and pharmacists involved in treatment decisions about the desired therapeutic profile for these populations is also important.

The results of this study will improve our understanding of treatment options for ageing people and will support evidence-based prescribing that addresses the complex needs of the ageing HIV population across the globe. By investigating key clinical outcomes, including mental health, sleep quality, and overall quality of life in these populations, these data could support clinicians in advancing personalised care for ageing people living with HIV.

4. Objectives

4.1. Primary objective

1. To describe detailed patient-reported outcomes before and after switch of HIV treatment in peri/post-menopausal and older adults, with a focus on sleep, mood, treatment satisfaction, and quality of life

4.2. Secondary objective

2. To explore the lived experiences of peri/post-menopausal and older adults who switch to B/F/TAF

3. To understand HIV clinicians' perceptions of the desired therapeutic profile and preferred treatment options and decision-making processes for older and peri/post-menopausal adults, as well as their experiences in relation to switch to B/F/TAF or alternative regimens

4. To determine clinical indications for switching treatment in peri/post-menopausal and older adults and the reasons for choice of treatment regimens in this population

5. To describe long-term clinical outcomes from routinely collected data from peri/post-menopausal and older adults receiving B/F/TAF in the United Kingdom

5. Outcome measures

Objective	Outcome measure/endpoints
1. **Patient-reported outcomes** (prospective PROMs cohort)	Change from baseline (pre- switch) to ~2 and ~6 months post-switch in a) Sleep quality (PROMIS) b) Mood (PHQ-9, GAD-7) c) Quality of life (HIVPROM) d) Treatment satisfaction (HIV TSQ) e) Frailty score (FRAIL scale)
2. Treatment durability	Proportion of participants who remain on B/F/TAF without discontinuation over 12, 24, 36, 48 and 60 months
3. Virological Efficacy (Routine data cohort)	a) Cumulative proportion of participants maintaining undetectable HIV viral load (<50 copies/mL) at 12, 24,36, 48 and 60 months post-switch (retrospective cohort) b) Cumulative incidence of virological failure over this time period will also be described
4. Safety Outcomes (Routine data cohort)	Described from start of regimen for the duration of follow-up in the routine data cohort: a) Change in renal function (eGFR) b) Change in bone density (by T score at hip and spine via DEXA scan, where available) c) Absolute change in weight and incidence of clinically significant weight gain (>5% baseline weight) d) Change in Hb1Ac and lipid profiles e) Change in CD4 T cell count
5. Frailty Measures (PROMs cohort)	Change in FRAIL Scale score from baseline to 6-months
6. Patient perceptions and lived experience (PROMs cohort)	Experiences and perceptions of B/F/TAF including tolerability, captured from in-depth semi-structured interviews with participants

7. Clinician perceptions and experiences	Focus groups with HIV clinicians (medics, pharmacist, nurse specialists) to understand for older and peri/post-menopausal adults: a) Desired therapeutic profile of ART regimens in this population b) Preferred regimens and experiences of B/F/TAF in this population c) Considerations discussed with individuals and the decision-making process in relation to switch to B/F/TAF or other regimens

6. Methodology

6.1. Study design

This is a multi-centre, mixed-methods observational study conducted at UK NHS HIV treatment centres, incorporating both prospective and retrospective components, alongside a nested qualitative element. The study is being coordinated by a research team at Brighton and Sussex Medical School which is part of the University of Sussex. The individual components of the study are described separately below, see Figure 1.

The study is formed of two sub-cohorts:

1) **A prospective PROMs cohort** of those who are switching HIV treatment as part of routine care, either to B/F/TAF or any other regimen (control), will complete PROMs on sleep, mood, frailty, quality of life and treatment satisfaction and a sub-sample will take part in an in-depth interview. Routinely collected clinic data will also be captured at key intervals until ~6 months post-switch.
2) **A routine data cohort** of those who have already switched to B/F/TAF prior to study enrolment, will have routinely collected clinical data captured from the most recent pre-switch medical records through to 5 years of B/F/TAF treatment, date of treatment discontinuation or study end.

6.2. Study population

The study will be conducted in NHS HIV departments in the UK with a diverse clinic population and will include adults with HIV-1. The entry criteria are based on age groups within which the syndromes of interest are prevalent. Around half of people

≥65 years have clinically detectable pre-frailty (35%) and frailty (13%) in the UK. The average age of menopause in the UK is 51 years of age, for the purposes of this study the perimenopause window is considered ≥40 years of age.

6.2.1. PROMs cohort eligibility criteria

6.2.2.1 Inclusion criteria

1. Adults with HIV-1

2. The potential participant has the mental capacity, and is willing to, provide informed consent to participate in the study.

3. The individual is planning to prospectively switch HIV treatment to either B/F/TAF or to an alternative ART regimen

4. The individual falls into one of the two populations of interest:
   a) Adults who are 60 years of age or older
   b) Individuals assigned female sex at birth who are between the ages of 40 to 60

6.2.2.2 Exclusion criteria

1. In the opinion of the research team the individual is unable or will be unwilling to comply with the study requirements

2. The individual has not provided informed consent

3. Data completeness is inadequate in the eyes of the site principal investigator

4. Pregnant at the time of eligibility assessment

6.2.2. Routine data cohort eligibility criteria

6.2.1.1 Inclusion criteria

1. Adults with HIV-1

2. The potential participant has the mental capacity, and is willing to, provide informed consent to participate in the study.

3. The individual is already receiving B/F/TAF, or has received B/F/TAF any time in the past

4. The individual falls into one of the two populations of interest:
    a. Adults who are 60 years of age or older
    b. Individuals assigned female sex at birth who are between the ages of 40 to 60

6.2.1.2 Exclusion criteria

1. In the opinion of the research team the individual is unable or will be unwilling to comply with the study requirements

2. The individual has not provided informed consent

3. Data completeness is inadequate in the eyes of the site principal investigator

4. Pregnant at the time of eligibility assessment

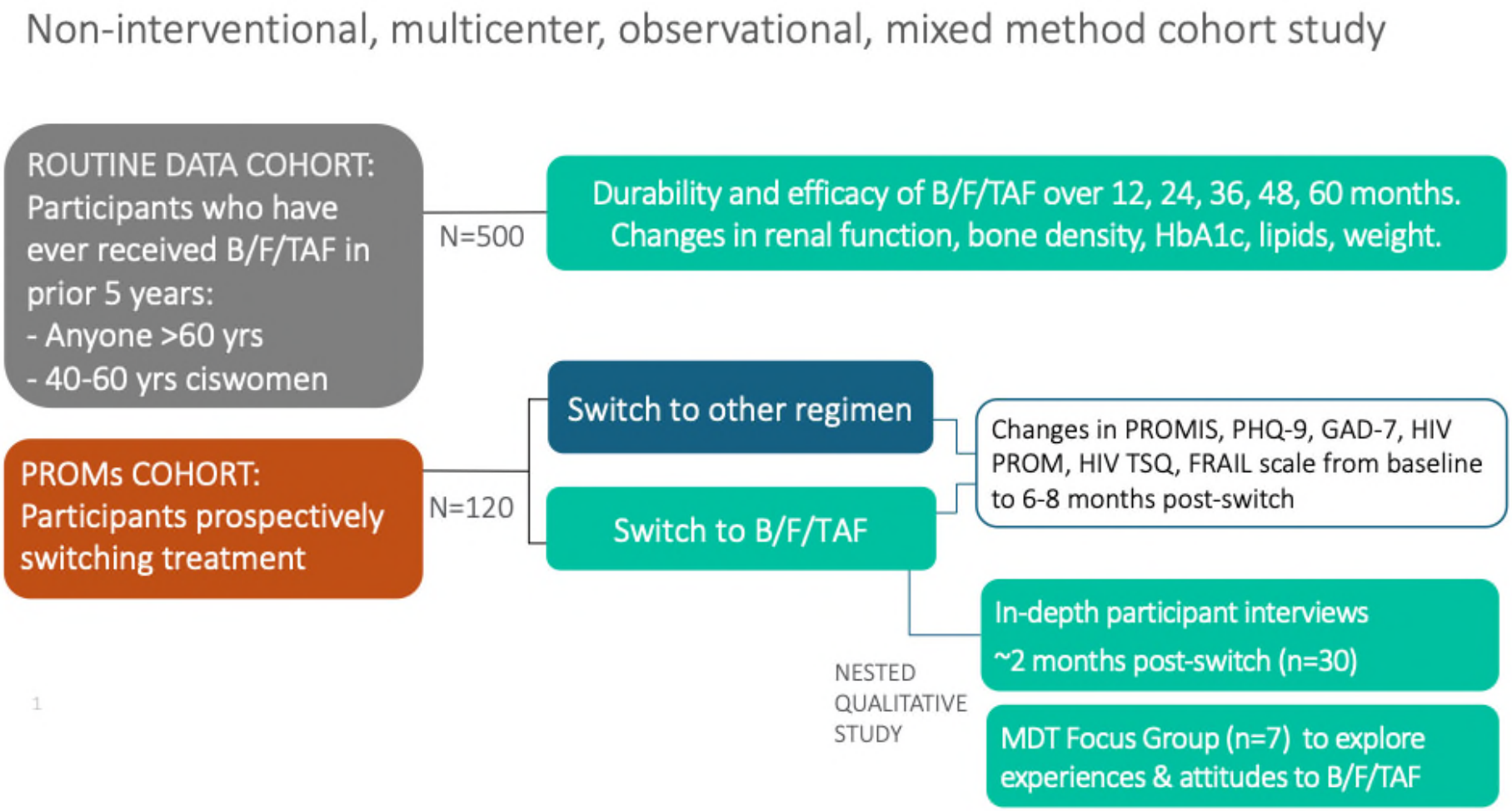


Figure 1. Full project overview

B/T/TAF, Bictegravir/emtricitabine/tenofovir alafenamide; PROMs, Patient reported outcome measure; MDT, multidisciplinary team

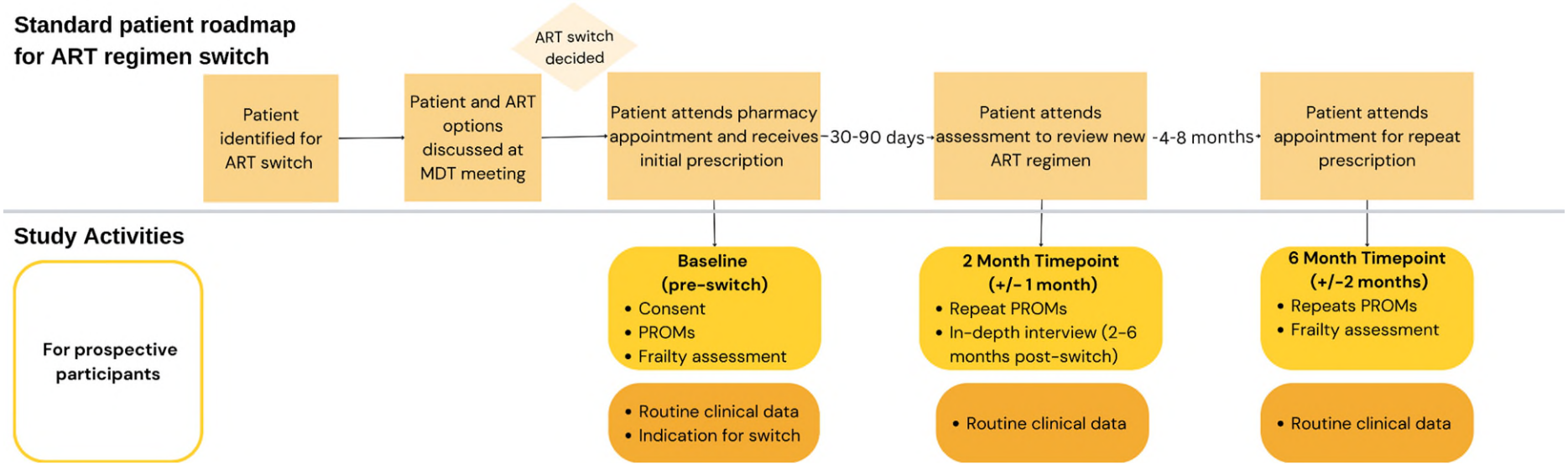


Figure 2. Project overview for PROMs cohort

6.3. Routinely Collected Clinical Data

The study will capture routine clinic data from eligible adults with HIV-1 receiving B/F/TAF as part of their treatment regimen, or who have received B/F/TAF any time in the past. Routine data will also be captured on eligible individuals who are due to switch to B/F/TAF (or other non-B/F/TAF regimens – control) prospectively

Routinely collected demographic and clinical data from eligible participants' medical records will be extracted at key intervals, as laid out in the Schedule of Activities (see section 7.3), and entered into an electronic data capture system (Research Electronic Data Capture, REDCap). Data will include demographics, HIV treatment history, laboratory results, and clinical events captured routinely in line with British HIV Association (BHIVA) monitoring guidelines.

Data will be collected at the following time points:

- Month 0 - most recent pre-switch record or from the day of switch
- 6 (+/-2) months post-switch
- Approximately 6 monthly thereafter until individual study end

For those in the routine data cohort: data will be collected at approximately 6-monthly intervals until treatment discontinuation, 5 years post switch to B/F/TAF or study end, whichever occurs first.

For those in the PROMs prospective cohort: data will be collected until ~6 months post switch.

6.4. Patient Reported Outcome Measures and Frailty Assessment (PROMs prospective cohort only)

Participants prospectively switching HIV treatment will complete the following PROMs:

- Patient Health Questionnaire-9 (PHQ-9)
- Generalised Anxiety Disorder-7 (GAD-7)
- PROMIS (sleep disturbance and sleep impairment)
- HIVPROM, HIV Treatment Satisfaction Questionnaire (HIV-TSQs)
- FRAIL Scale
- Menopause rating scale (MRS) (individuals assigned female sex at birth only)

PROMs will be completed by self-administered REDCap forms with assistance from the research team where required.

The collection of PROMs and frailty data will occur at baseline (pre-switch), month 2 (+/-1) and again at 6 (+/-2) months post-switch, in line with routine clinic visits (see Schedule of Activities). These measures are collected prospectively because detailed data on mood, sleep, treatment satisfaction, and frailty are not routinely captured in standard clinical care, meaning retrospective collection of this data is likely to be subject to recall bias.

The routine data cohort will not complete PROMs or frailty assessments.

A comparator group on other oral ART regimens will also be invited to join the study. Eligible individuals switching to any other oral ART regimen for any reason within the study period are eligible to participate. The B/F/TAF group and the 'other ART' group will be recruited in a 1:1 ratio as guided by the coordinating centre.

6.5. Nested qualitative sub-study

We will explore patient and clinician perspectives on HIV treatment in the peri/post-menopause and later life through a nested qualitative study. Semi-structured interviews (patient participants) and focus groups (HIV clinicians) will be audio-recorded, transcribed verbatim and analysed using reflexive thematic analysis.

6.5.1. Patient interviews (prospective B/F/TAF group)

A purposive subsample (~20–30 participants across sites until thematic saturation is achieved) will be interviewed 2-6 months post-switch to capture experiences (e.g. relief of prior ART side-effects, new adverse effects, and considerations around switch/discontinuation).

6.5.2. HIV clinician focus groups

One focus group will be conducted per collaborating NHS Trust with at least 3 key MDT members (e.g. HIV physicians, pharmacists, nurse specialists) involved in ART switch decisions (total participants, n = 18-24). Discussions will examine the desired therapeutic profile in peri/post-menopausal and older adults, preferred regimens and experiences of B/F/TAF in this population, considerations discussed with individuals and the decision-making process in relation to switching.

6.5.2.1 Inclusion

1. Any healthcare professional working within the HIV clinic site who is involved in ART switch decisions or discussions with patient
2. Willing to participate in a focus group with other MDT members

6.5.2.1 Exclusion

1. Not employed within the collaborating NHS Trust's HIV service or not involved in ART switch decisions/discussions in routine care.
2. Unable to give informed consent or unwilling to be audio-recorded.
3. Insufficient English proficiency to take part in a group discussion

7. Study procedures

7.1. Identification of potential participants

Potential participants for either cohort will be identified by the site HIV research team. They will be approached by their HIV clinician and/or a local research team member (in person, by phone, or by email) and given a brief explanation of the study. Interested individuals will receive the Participant Information Sheet (PIS) relevant to the sub-cohort they are eligible to join either in person/paper or electronically.

7.2. Informed consent

Participants who are interested in taking part will be given the opportunity to ask any questions once they have read the PIS. If they would like to take part, individual consent will be obtained before any study procedures take place. The local research team will confirm eligibility, including capacity to consent, and potential participants will be invited to complete the informed consent form (ICF) either in person (paper) or electronically, depending on preference. Signed consent forms will be filed locally and the coordinating centre notified.

7.2.1. Qualitative sub-study informed consent

A separate consent process, conducted by the Brighton and Sussex Medical School (BSMS) coordinating team, will cover in-depth interviews (people with HIV) or focus groups (HIV clinicians) from each NHS site. Participants will be provided with a qualitative study-specific PIS and given the opportunity to ask any questions. A separate consent form will also be provided and participants will be asked to sign this either electronically or in-person (paper) depending on preference.

7.3. Collation of routinely collected clinic data

Routinely collected clinic data from all participants will be submitted by the participating clinic investigator (research nurse or research assistant) via a REDCap case report form or by electronic patient record download. Routine blood testing is performed as part of routine clinical care per the BHIVA HIV Monitoring Guidelines (9). No research blood testing is performed.

Follow-up for each participant will start on the day of initiating B/F/TAF. For the routine data cohort, follow-up will end on the date that the regimen is discontinued, after 5 years of B/F/TAF treatment, or at the overall study end date, whichever comes first. For the PROMs prospective cohort the follow-up will end after the 6-months PROMs and routine data entry have been completed.

Data to be collected by local research team:

- **Demographic and basic information:** date of birth, sex at birth, gender identity, country of origin, ethnicity, height, date of first HIV-1 positive test and mode of HIV-1 transmission, post code, employment status. Collected once, following participant consent
- **Laboratory data and weight:** weight, CD4+ T cell count, HIV viral load, creatinine, lipids, HbA1c, ALT, DEXA T score at hip and spine.
- **Medical history and concomitant medication:** medical comorbidities, number of concomitant medications, statin therapy, hormone replacement therapy, antihypertensive therapy, antidiabetic therapy.
- **HIV treatment:** HIV regimen before, and after switch to B/F/TAF, total number of regimens and drug classes received
- **Clinical Events:** Drug-related clinical events

Table 1. Schedule of activities for routine data cohort

Schedule of Activities	**Individual baseline month 0*** (at the time of switch or preceding visit)	**Individual month 6 (+/- 2)**	**Every ~6 months until individual study end**
ROUTINELY COLLECTED CLINIC DATA			
Informed consent process	X		
Baseline characteristics, height	X		
Frailty status (where available)	X		
Last menstrual period (where applicable and available)	X		
Indications for switch to B/F/TAF and reasons for discontinuation (where applicable)	X		
Comorbidities including falls	X	X	X
HIV history	X		
ART history	X		
HIV VL (all interim VLs collected)	X	X	X
CD4+ T cell count (if available)	X	X	X
Weight (kg, if available)	X	X	X
Creatinine, HbA1c, lipids, ALT, bone density T score at hip and spine (if available)	X	X	X
Concomitant medications including hormone replacement therapies	X	X	X
Drug-related interim medical events		X	X

7.4. PROMs and frailty assessment (PROMs prospective cohort)

In the prospective cohort, as well as capturing routine data, individuals will be asked to complete the following PROMs as per Table 2:

- Patient Health Questionnaire-9 (PHQ-9)(18),
- Generalised Anxiety Disorder 7-item (GAD-7)(19),
- PROMIS (sleep disturbance & sleep impairment)(20),
- HIVPROM(21),
- HIV Treatment Satisfaction Questionnaire(22).
- FRAIL scale (25)
- Menopause Rating Scale (MRS) (individuals assigned female sex at birth only) (26)

Participants will be sent on-line REDCap questionnaires to complete themselves at three timepoints: baseline (pre-switch), and at 2 and 6 months following switch. If the participant is unable to directly enter data on the REDCap questionnaires the data from a paper-based questionnaire can be entered into REDCap on behalf of the participant by a member of the study team.

Table 2. Schedule of activities for PROMs prospective cohort

Schedule of Activities	**Individual baseline month 0*** (at the time of switch or preceding visit)	**Individual month 2 (+/-1)**	**Individual month 6 (+/- 2)**
Informed consent process	X		
ROUTINELY COLLECTED CLINIC DATA			
Baseline characteristics, height (cm)	X		
Frailty status (where available)	X		
Last menstrual period (where applicable and available)	X		
Indications for switch and reasons for discontinuation (where applicable)	X		
Comorbidities including falls	X	X	X
HIV / ART history	X		
Weight (kg)	X		X
HIV VL	X	X	X
CD4+ T cell count (if available)	X	X	X
Creatinine, eGFR, HbA1c, lipids, ALT, weight, bone density T score at hip and spine (if available)	X	X	X
Concomitant medications including hormone replacement therapies	X	X	X

Drug-related interim medical events		X	X
QUESTIONNAIRES			
• HIV PROM • PHQ-9 (if not already done in routine care) • GAD-7 (anxiety) • PROMIS (sleep disturbance & sleep impairment) • HIV Treatment Satisfaction Questionnaire (HIVSTQs12 at baseline/2 month and HIVTSQc12 at M6 only) • Frailty assessment: FRAIL scale • Menopause rating scale (MRS) (individuals assigned female sex at birth only)	X	X	X
QUALITATIVE			
In-depth interviews (n=3-4 per site)		X	

7.5. Nested qualitative study

7.5.1. Participant interviews (prospective PROMs sub-cohort)

A subset of people in the prospective PROMs cohort study at each site will be approached to consent for an in-depth interview about their experiences after receiving approximately 2-6 months of treatment with B/F/TAF. They will be purposively sampled by age, gender, duration of HIV diagnosis, ethnicity and sexual orientation. The in-depth interviews will be conducted by a research assistant from BSMS at the University of Sussex. Site teams are required to identify participants and gain permission for the research team at BSMS to contact them. An additional consent process will be undertaken by BSMS research staff prior to conducting the interview and consenting individuals will be interviewed on-line or via telephone (depending on participant preference) from a quiet room at Brighton and Sussex Medical School. Interviews will take a maximum of 1 hour and will be audio-recorded then transcribed and anonymised for analysis. It is anticipated that interviewing approximately 3-4 individuals at each site will reach thematic saturation. Where interviews cannot be conducted on-line then a member of the research team can support an in-person interview. A study participant will only be interviewed once during their follow-up period. Anyone interviewed will be remunerated with a £20 shopping voucher or bank transfer to compensate for their time and effort.

7.5.2. Healthcare provider focus groups

We will conduct focus groups with key healthcare workers responsible for delivering the switch service at each clinic including an HIV/ID Consultant, Clinical Nurse Specialist and Pharmacist or any other member of staff involved with HIV treatment decisions. The focus group can take place at any time point during the study site participation in the study. An on-line consent process will be completed prior to any focus group taking place via MS Team from a private room at Brighton and Sussex Medical School. Personal data will be anonymised.

7.6. Safety reporting

7.6.1. Safety reported - HRA requirement

As a non-clinical trial of investigational medicinal products (CTIMPS) study, reports of Serious Adverse Events (SAEs) that are:

- **related** to the study (i.e. they resulted from administration of any of the research procedures) and
- **unexpected** (i.e. not listed in the protocol as an expected occurrence)

Should be emailed to the REC and the study sponsor using the Non-CTIMP safety report to REC form (available on the study REDCAP account or from the central study team).
These should be sent within 15 days of the chief investigator becoming aware of the event.

7.6.2. Safety reporting – funder requirement

The study funders have requested additional safety reporting be followed.

If a serious adverse event (SAE) has occurred during the participant follow up period and the SAE is **possibly, probably or definitely related to B/F/TAF or study procedures (i.e. a suspected serious adverse reaction)** it should be reported to the Gilead safety team as soon as possible in the interest of pharmacovigilance. The definition of possible, probable or definitely related events is shown below.

7.6.2.1 Assessing adverse events for seriousness, causality and expectedness

A serious adverse event is any untoward medical occurrence that meets one of the following criteria:

1. fatal
2. immediately life-threatening
3. results in hospitalisation or a prolongation of an existing hospitalisation (does not include visits to A+E without admission, admissions for social reasons or elective procedures for cosmetic surgery).
4. abnormal pregnancy outcome
5. causes severe disability/incapacity

The causality of the SAE should be assessed when deciding whether to report the SAE to the Gilead safety team. If any doubt exists then please discuss with the site Principal Investigator.

Causality of adverse events	
Unrelated	No evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after a study procedure). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after a study product/procedure). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship with study product/procedures and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship with study product/procedures and other possible contributing factors can be ruled out.

Expectedness of the event in relation to B/F/TAF or underlying disease (HIV or associated comorbidities) must then be determined. Expected side effects from the product are listed in the summary of medical product characteristics (SmPC).

If an SAE is deemed to be related to B/F/TAF and unexpected according to the SmPC then this is considered a suspected unexpected serious adverse reaction (SUSAR), which requires expedited reporting and a high level of scrutiny.

The SAE reporting process will be performed by the Chief Investigator following discussion with the participant's responsible clinician who is likely to have the best understanding of the participant's medical history, the event and its clinical course. The safety reporting form is in the Appendix. It should be reported to the Gilead safety team within 24 hours of the site research team becoming aware of the event.

8. Risks and benefits for participants

8.1. Risks

Participation in this study does not include any risk for the participants as the study does not test any drugs and participation in this study does not interfere with the treatment/care participants may receive at their regular HIV clinic. Within the HIV service clear pathways for the management of medical complications exist and all issues will follow these pre-defined pathways. However, participants may find the questionnaire tiring or they may cause fatigue. Participants will be able to complete questionnaires at their own pace and with the help of a member of their HIV care team if required.

8.2. Benefits

There are no direct benefits to the participants. However, the benefit of conducting observational research includes advancing scientific understanding of how different ART benefits different patient populations; this knowledge may guide treatment recommendations to the benefit of people living with HIV.

9. Withdrawal from study

Withdrawal from the study may be required if the participant withdraws consent as they no longer wish to participate. The decision to withdraw and the reason will be documented in the eCRF. The participant will be informed that data and samples collected up to that point will be retained for the purposes of the study, with their permission.

If a participant is lost to follow-up they can remain in the cohort and their missed visits will be documented in the eCRF. It is important to allow data collection on these individuals in case they return at a later date as describing their outcomes is of interest.

If an individual transfers out to another clinic it may not be possible to collect their routine clinic data (e.g. viral load data) however they can still complete questionnaires and therefore can remain in the cohort. The reason the laboratory data is missing will be recorded in the eCRF.

10. Ethical Considerations

10.1. Approvals

The investigator(s) will ensure that this study is conducted in full conformity with the 7th revision of the 1964 Declaration of Helsinki. The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines and Addendum ICH GCP E6 (R2)).

Prior to the enrolment of participants, the Sponsor's research ethics committee (REC) and the Health Regulatory Authority (HRA) must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheets and Informed Consent Forms, any other written information that will be provided to the participants, any advertisements that will be used and details of any subject compensation.

Any proposed amendments to the protocol or informed consent forms must be submitted to the sponsor for approval. Following which REC for approval can be sought and may be implemented only after REC approval has been obtained. The amended protocol will be sent to participating sites for local approval to be granted and the approved version will be shared with all staff involved in the study.

HRA approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing. The HRA and all participating sites also need to be notified of all protocol amendments to categorise the amendment and assess whether the amendment affects the institutional approval for each site.

The REC will be informed about study progress in line with HRA recommendations.

10.2. Compliance

Deviations from research protocols and GCP occur commonly, the majority of these instances are technical deviations that do not result in harm to the participants or significantly affect the scientific value of the reported results of the trial. Protocol deviations (PD) or violations (PV) should be documented in the deviation case report form in REDCap in order for corrective and preventative actions to be taken.

The Investigators will review all PDs and PVs and these will also be reported to the Sponsor. It is the responsibility of the Sponsor to assess the impact of the breach on the scientific value of the and an assessment of whether the PV constitutes a serious breach will be made.

A serious breach is defined as a breach of the principles/conditions of GCP, or of the trial protocol, that affect to a significant degree the safety of study participants or the scientific value of the trial. The Sponsor should be notified within 24 hours of identification of a serious breach. The judgement on whether a breach is likely to have a significant impact on the scientific value of the trial depends on a variety of factors e.g. the type and extent of the data affected by the breach, the overall contribution of the data to key analysis parameters, the impact of excluding the data from the analysis etc. Examples of serious breach:

- Breach of GCP or protocol leading to the death, hospitalisation or permanent disability of a participant
- Proof of fraud relating to clinical trial records or data
- Persistent or systematic non-compliance with GCP or protocol that has a significant impact on the integrity of trial participants in the UK
- Failure to comply with safety reporting requirements.

The Sponsor will notify REC within 7 days of becoming aware of a serious breach.

10.2.1. Insurance and Indemnity

The University of Sussex has indemnity cover in place which may respond to its legal liabilities in respect of this study.

10.3. Informed consent process

Informed consent will be obtained from all participants using REC approved Participant Information Sheet(s) (PIS) and Informed Consent Form(s) (ICF).

The participant will be informed about the rationale and requirements of the study via the electronic PIS. Or where there are any reading difficulties, or if the potential

participant has questions, the PIS can be downloaded and printed and an in-person consent process with the research team can be completed.

Potential participants will be given an adequate amount of time to consider their participation in the study. If they decide to participate in the study they will be asked to sign the ICF on-line, which will then be countersigned by the site Investigator. The participant will be emailed a copy of the signed ICF, another copy will be downloaded and filed in the participant's research records at the site.

The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment.

10.4. Confidentiality

The Investigators must ensure that the participant's confidentiality is maintained in accordance with Good Clinical Practice (GCP) Guidelines. Study participants are de-identified and anonymised with a Unique Patient Identifier (PID). A de-coding list is held in a safe location by the individual site and it is the responsibility of cohort PI/local study staff to secure this. All data shared will contain the PID number and no unique person identifiers. On the eCRF or other documents submitted to the Sponsor, the participant will be identified by a participant ID number only. Only the Central Data Manager will have access to the participant ICF where the name is evident.

The Investigator shall permit direct access to participants' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor and REC.

10.5. Data Protection

The investigator will preserve the confidentiality of all participants taking part in the study, which will be conducted in accordance with the General Data Protection Regulation (GDPR). The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

11. Remuneration

Participants are not remunerated for joining the retrospective study, as no study activities outside of consenting to the collection of their routine data is required. However, participants joining the prospective sub-cohort will be remunerated with a £20 voucher for completing the questionnaires at each timepoint. Additionally, those who take part in the in-depth interview will also receive a £20 voucher in recognition of their time.

There is no remuneration for clinicians participating in this study.

12. Data Management

The research tools and eCRFs are in English or Welsh. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood, and be in the language appropriate for the study site.

12.1. Source data

Source documents include original documents related to the study data (e.g. patient medical records which can be paper-based or electronic). Adequate source documentation must be maintained at participating sites to allow reliable verification and validation of the study data.

For questionnaires that are administered directly on-line the eCRF is the source document.

12.2. Data Collection and Database

Study data will be collected on an electronic case report forms (eCRFs) or via data download to MS Excel spreadsheet. The principal means of data collection from participant visits will be Electronic Data Capture (EDC) using the REDCap database. Data are entered into REDCap system by trained site personnel. Data entered by the site team will include demographics, medical history, HIV treatment history, blood test results, protocol deviations etc.

The participants will be sent on-line REDCap questionnaires at month 0, month 1-2, and months 6-8 and by answering the questions it will be directly entered into REDCap. If the participant is unable to directly enter data on the REDCap questionnaires the data from a paper-based questionnaire can be entered into REDCap on behalf of the participant by a member of the study team.

All changes made following initial submission of data will have an electronic audit trail with a date. Specific instructions and further details will be outlined in the study specific eCRF completion manual.

12.3. Data storage and archiving

The investigator must retain essential documents until notified by the Sponsor, and for at least ten (10) years after study completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor. All data collected during the study will be stored in the UK.

Data is held securely by the Sponsor for at least 10 years on a password-protected electronic folder in the University of Sussex hosting service (One Drive).

12.4. Data sharing

We will be proactive in ensuring that this valuable data is used to its full potential. The Study Management Group (SMG) will welcome proposals for collaborations from other academic groups as well as the study funders. Those potentially interested should submit a proposal to the SMG containing information about the project, analysis plan and data requirements. Proposals will then be discussed by the SMG and will be approved if it is felt to be scientifically valid with appropriate methodology. Any request for sharing the study dataset must be approved by the SMG.

13. Statistical considerations

As this is primarily a descriptive study no formal power calculation is required. The inclusion of a group of people receiving non-B/F/TAF oral ART is to give an indication of the outcomes that would be seen had the participant not switched to B/F/TAF, but it is not our intention at this stage to formally compare groups due to the expected differences in characteristics of the two groups.

Detailed description of the statistical analyses, any deviation from the protocol, and assumptions employed will be presented in a detailed Statistical Analysis Plan (SAP) that will be prepared prior to database closure and initiation of any statistical analyses below.

Follow-up for each individual will start on the day of initiating B/F/TAF and will end on the date that the regimen is discontinued, after 6 months (prospective component) or 5 years (retrospective component), or on the study follow-up end date whichever comes first.

Descriptive statistics (mean/SD, median/IQR, n (%)) will be used to describe baseline demographics and HIV-specific factors (duration of diagnosed HIV infection, nadir CD4+ T-cell count, duration of ART prior to day of switch (day 1), duration of virological suppression prior to day of switch (day 1)).

Patient-reported outcomes will be analysed as changes scores (PROMIS, PHQ-9, GAD-7, HIV PROM, HIV TSQ) between baseline (before initiating B/F/TAF) to 2 and 6 months post-switch in the participants in the prospective component with comparison between the B/F/TAF and the control groups. Generalised linear regression will be used with appropriate adjustment for confounding factors.

Treatment durability and tolerability will be described as the cumulative proportion of participants who remain on B/F/TAF without discontinuation due to adverse events over 12, 24, 36, 48 and 60 months retrospective component.

Efficacy will be described as the cumulative proportion of participants maintaining undetectable HIV viral load (<50 copies/mL) at 12, 24,36, 48 and 60 months post-

switch (retrospective component). Cumulative incidence of virological failure over this time period will also be described.

Safety endpoints will be described at 12-month intervals post-switch for duration of follow-up for the retrospective component. Change in eGFR, bone density, HbA1c, CD4 T cell count will be analysed using general linear regression adjusted for confounding factors. Proportion experiencing clinically significant weight gain will be described.

Frailty endpoints in the prospective component will be analysed as change in FRAIL Scale score between baseline and 6 months using general linear regression adjusted for confounding factors.

Qualitative data from in-depth interviews and focus groups will be audio-recorded and transcribed. Data will be analysed using reflexive thematic analysis, informed by Braun and Clarke's (2006/2019) (23, 24)six-phase process.

The 'end of study' is the point at which last participant final visit individual data has been entered into the electronic data capture system and all the qualitative work has been completed. Thereafter, the 'end of study' the close out visit will be performed. The study will only be considered 'closed' when all participants have completed their final study visit, all assessments completed, all the data have been entered into the database and all data queries resolved, close out visit conducted, the database locked and data analysis performed and reports written.

14. Study Management and Oversight

The study has undergone independent peer review at the Protocol Review Panel at University of Sussex.

The study will be managed via the Brighton and Sussex Medical School Department of Global Health and Infection at the University of Sussex. The study management group (SMG) consisting of the Chief Investigators, Co-Investigators, Study Manager and Data Manager, and will be responsible for the day-to-day conduct of the study and will troubleshoot any operational issues.

As this is a low-risk non-interventional protocol, there is no requirement for a data safety monitoring committee for this study. University of Sussex safeguarding policies will be followed https://www.sussex.ac.uk/safeguarding/.

The sponsor will be notified of study progress including end of study and study closure.

The sponsor, University of Sussex, will assume overall responsibility for the proportionate, effective arrangements being in place to set up, run and report the research project.

14.1. Monitoring

The study will be monitored periodically by study monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

14.2. Audit

The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection. The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the The UK policy framework for health and social care research (2017).

14.3. Public Involvement

Members of the public are actively involved in the creation of the protocol, participant information sheets and informed consent forms. Community events will be organised over the course of the study to ensure that findings are shared in an appropriate format and that public advice on suitable dissemination strategies is sought.

15. Publication Policy

Information concerning the study, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purposes of the study only. All information obtained as a result of the study will be regarded as confidential, at least until appropriate analysis and review by the investigator(s) are completed.

Study results will be published in peer-reviewed journals and will be presented at national and international meetings. Publication will be in accordance with international recognized scientific and ethical standards concerning publications and authorships. We will ensure that all relevant stakeholders receive information on study outcomes. Full anonymity of participants'' details will be maintained throughout, and no individual patient data will be presented.

A full publication policy, including timelines for receipt of feedback and guidelines for authorship will be drafted.

16. Conflicts of Interest

The study is funded by Gilead Sciences Ltd who manufacture B/F/TAF

17. Support Sources

- **Terrence Higgins Trust (THT Direct)**
  Phone: 0808 802 1221 (free)
  Web: tht.org.uk
  What they do: HIV info, testing, and support; can signpost to local services.

- **Samaritans (24/7 emotional support)**
  Phone: 116 123 (free, UK & ROI)
  Email: jo@samaritans.org
  Web: samaritans.org

- **Shout Crisis Text Line (24/7)**
  Text: SHOUT to 85258 (free, UK)
  Web: giveusashout.org
  What they do: Emotional support, help to de-escalate, think through options, signposting

- **Local HIV clinic**
  Best quick routes:
  • Call NHS 111 (24/7) and ask for your nearest HIV clinic, or
  • Use the NHS service finder at nhs.uk (search “HIV clinic” or “sexual health services”) to get the address/phone for your area.

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