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Qualitative study exploring the experiences and perceptions of dolutegravir/lamivudine dual antiretroviral therapy (the PEDAL study) in people living with HIV: protocol

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ABSTRACT

Introduction Antiretroviral treatment turned HIV infection into a chronic disease and improved quality of life for people living with HIV. Dual-drug combinations have been shown to be effective in suppressing viral replication and can potentially reduce long-term drug-associated toxicities. We aim to investigate patients' perceptions and experiences on the safety, effectiveness, tolerability and unmet needs of the dual-drug combination dolutegravir/lamivudine in Brighton and Hove, UK. In addition, we will conduct a comparative analysis between patients on dolutegravir/lamivudine and patients on other dual-drug and three-drug combinations. Finally, the study aims to provide recommendations to improve doctor–patient communication, knowledge and understanding of the treatment plan, and additional care that ought to be considered in patient-centred, holistic care plans.

Methods and analysis Our qualitative methodological framework is based on three main methods: cultural domain analysis, focus group discussions and in-depth interviews. Cultural domain analysis employs a range of techniques (free listing, pile sorts and rankings) to elicit terms from informants regarding specific cultural domains (ie, groups of items that are perceived to be of the same kind). This framework has been codesigned with a patient representative to ensure relevance, suitability and coproduction of knowledge. All methods have been tested to take place online, as an option, via Zoom, Skype or Microsoft Teams. Padlet, an application to create online boards, will be used during the cultural domain analysis session. Data collected will be analysed following the completion of each method embracing an iterative approach through applied thematic analysis.

Ethics and dissemination Ethical approval was obtained from the Health Research Authority (Reference 21/NW/0070). Findings will be used to produce recommendations to improve doctor and patient communication by identifying patients' fears, worries, misconceptions and general concerns of their drug regimen. Conclusions will be disseminated via journal articles, conference papers and discussions through public engagement events.

STRENGTHS AND LIMITATIONS OF THE STUDY

⇒ This study is the first of its kind to provide patient-centred insight into dolutegravir/lamivudine through an in-depth qualitative, iterative and comparative approach that applies the use of three research methods (cultural domain analysis, focus group discussions and in-depth interviews).
⇒ The study's protocol has been codesigned with a representative of people living with HIV in Brighton and Hove to ensure coproduction of knowledge.
⇒ The possibility of taking part in research both in-person and online will allow for increased anonymity and flexibility for patients to participate while simultaneously ensuring that they are safe in the COVID-19 environment by reducing in-person meetings.
⇒ The HIV cohort in Brighton and Hove might not be representative of the whole country and groups like women, ethnic minorities and transgender individuals might be underrepresented.
⇒ Potential participants who might not feel comfortable meeting in person and who lack the digital skills required might be unable to take part in the study.

Project registration number IRAS number: 286277. NCT04901728.

INTRODUCTION

Dolutegravir (DTG), an integrase strand transfer inhibitor (InSTI), is currently recommended for both treatment initiation and second-line/third-line therapy for people living with HIV-1 (PLWH), in combination with either tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), tenofovir alafenamide (TAF/FTC) or abacavir/lamivudine (ABC/3TC).[1–3] DTG has a high genetic

barrier to resistance, and DTG-based dual-drug regimens, by maintaining the robustness and potency of DTG-based three-drug regimens, have the potential advantage of reducing the risk of long-term cardiovascular (ABC) or renal/bone drug-mediated toxicity (TDF).[4] The dual-drug combination DTG/3TC has proven non-inferior to the triple-drug combination TDF/FTC/DTG in the GEMINI-1 and GEMINI-2 trials for the treatment of antiretroviral treatment (ART) naïve individuals.[5] Treatment guidelines of the European AIDS Clinical Society, of the US Department of Health and Human Services and of the International Antiviral Society–USA Panel have introduced this option among recommended first-line regimens, providing the patient HIV-1 RNA is<500 000 copies/mL and the CD4 count>200 cells/mm^3.[1 2 6] Based on the results of the ASPIRE,[7] LAMIDOL[8] and, ultimately, TANGO studies,[9] the dual-drug combination DTG/3TC has also proven to be a safe and effective option for treatment simplification of ART-experienced suppressed individuals on triple-drug therapy. A recent systematic review and meta-analysis explored real-world effectiveness and tolerability of DTG/3TC in virologically suppressed patients and documented long-term virological outcomes consistent with findings from randomised clinical trials.[10]

Although there is clinical evidence of the safety, effectiveness and tolerability of dual-drug regimens,[11–16] there is limited insight into patient experiences and perceptions of dual-drug combinations, including the DTG/3TC regimen. A qualitative study conducted in the USA and in Spain explored patients' perspectives and experiences in 39 patients on dual-drug combinations and documented that participants viewed dual-drug regimens as a significant and positive advance, in terms of its effectiveness, with reduced toxicity and essentially no reported side effects.[17] The study highlighted the central role of healthcare providers in the decision to switch to dual-drug combinations. Further evidence on quality of life comes from a Swiss trial evaluating the efficacy of the dual-drug regimen DTG+FTC: in the DTG+FTC arm, quality of life, assessed via the PROQOL-HIV questionnaire, improved significantly more than in the control, triple-drug arm.[16] With the advent of long-acting dual-drug combinations (cabotegravir/rilpirivine (RPV)),[18] patients' insights and perceptions of dual regimens are timely and needed.

The PEDAL study aims at exploring patients' experiences and perceptions of the dual-drug regimen DTG/3TC, including potentially unmet treatment needs and reported outcomes for those already on this combination. In addition, we will conduct a three-phase comparative study with a comparison population alongside the target population (figure 1). The comparison population will include PLWH on dual-drug regimens other than DTG/3TC and a group on triple-drug therapy. In the comparison group of participants receiving dual-drug therapies, we will include patients (a) on DTG/RPV, (b) on boosted-darunavir plus lamivudine (DRV/ritonavir[r] or DRV/cobicistat[c] + 3TC) and (c) on boosted-darunavir plus raltegravir (DRV/r or DRV/c + RAL). The addition of the comparison group of patients on other dual-drug therapies will allow us to tease out the particular characteristics of DTG/3TC beyond the mere reduction of molecules employed for the treatment. This study will be the first of its kind to provide patient-centred insight into this specific treatment combination and to produce recommendations for improved clinical care.

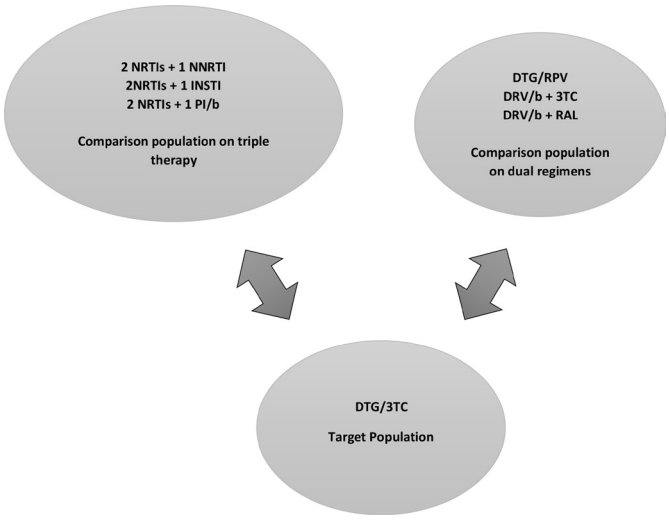

Figure 1 Comparison populations and target population.

Aims and objectives

This research will use a qualitative methodology to explore patients' perceptions and experiences of the dual-drug treatment regimen DTG/3TC, including potentially unmet treatment needs.

The objectives are as follows:

- To investigate patients' perceptions and experiences of the safety, effectiveness, tolerability and unmet needs of DTG/3TC.
- To conduct a comparative analysis of the safety, effectiveness, tolerability and unmet needs between patients on DTG/3TC and patients on other dual-drug and three-drug combinations.
- To provide recommendations to improve doctor–patient communication, knowledge and understanding of treatment plans and additional care to be considered in patient-centred, holistic care plans.

Research questions

- What are patients' experiences and perceptions of the safety, effectiveness, and tolerability of DTG/3TC?
- What are the unmet needs of patients taking DTG/3TC?

Theoretical approach

The theoretical framework that informs this study is rooted in Critical Medical Anthropology (CMA). Central to the CMA approach to the study of health and disease is (1) close attention to 'ecological, biological and cultural factors;' (2) consideration of the 'political and economic forces that influence disease patterns and affect access

to healthcare resources;' and (3) the 'opportunity for health-promoting interventions'.[19]

CMA can provide crucial information on environments of risk that contribute to individual diseases as well as syndemics (sets of interactive problems) and it can provide insight into networks of communication and trust that connect people.[20] CMA differs from the public health theory Social Determinants of Health (SDH), whose approach tends to ignore the political economy of health, which is central to CMA. Factors often identified as SDH include poverty, (un)employment, stress, inequalities in housing, education, social inclusion, nutrition and lifestyle factors like ethnicity and sexual behaviour.[21] In contrast, CMA both identifies such factors, and also attempts to understand their broader context and causes. The CMA approach will allow the study to take the social systems in which patients and medicines move to be embedded with and in interaction with the political and economic structures that order our world.[22] Medicines are social objects that this study follows to reveal individual perceptions and experiences of treatment, as well as support networks and patient–provider relationships all located within a complex world order.

In this research, medicines are taken to be material things that have 'biographies' or social lives as they move through different settings and are attributed value as individual things or as commodities for exchange.[23] Following Whyte *et al*,[24] the research is concerned with the social uses and consequences of medicines, specifically DTG/3TC. Medicines have relationships 'with people and between people' and are the 'most personal of material objects' with the power 'to transform bodies'.[24] They 'can be simultaneously noxious and beneficial'.[24] Therapeutic functions of medicines will not be overlooked, but the study will draw attention to the aspects of medicines that tend to be overlooked.[25] This research pays attention to the non-medical meanings and effects of medicines by understanding how DTG/3TC, and the comparison regimens, mean different things and serves different interests to different people in different situations.[25]

In undertaking a study of patient perceptions and experiences of DTG/3TC, the study will explore patients' own rationalities for use of medicines. It will also attempt to understand how patients perceive and experience the efficacy of DTG/3TC while accounting for local and individual contingencies that influence efficacy. What works for one person might not work for the next, and different dosages, timings and ways of taking medicines are tinkered with by healthcare professionals and patients on a case-by-case basis.[26] Additionally, safety of DTG/3TC must be understood in relation to patient vulnerability, particularly in relation to their own situation. What the study hopes to show is that to truly explore the study variables (tolerability, efficacy and safety) medicines must be taken to be social objects while also locating the study of HIV in broader structures that guide daily lives.

In conclusion, by adopting this theoretical framework, the study can best understand the tolerability, safety, efficacy and unmet needs of DTG/3TC both as defined by biomedical science, and also through an understanding of patients' perceptions and experiences. CMA allows us to factor in broader structural issues that might impact patient circumstances and thus influence their perceptions and experiences of or on DTG/3TC. While simultaneously taking medicines to have social lives allows us better to understand the relationship individual patients have with DTG/3TC and the ways that patients speak between themselves about it.

METHODS AND ANALYSIS

Study design

The PEDAL study, funded by ViiV Healthcare, is a qualitative study containing in-built elements for continuous data analysis based on an iterative approach. This will allow us to continuously refine our methodological framework following the implementation of each method. Data collection for this study commenced in June 2021 and is expected to be finalised by June 2022. We will engage with a target population (patients on DTG/3TC) and two comparison populations (patients on other dual-drug regimens and triple-drug ART) through cultural domain analysis (CDA), focus group discussions (FGDs) and in-depth interviews (IDIs). On completion of data collection, applied thematic analysis (ATA) will be used to identify emerging themes.

Patient and public involvement

The study's protocol has been codesigned with a representative of PLWH in Brighton and Hove to ensure coproduction of knowledge. Recruitment of patients will take place both at the clinical facilities and via peer support groups (see below). Members of the community will be invited to attend public engagement events organised by The Sussex Beacon and the Brighton and Sussex Medical School (BSMS).

Recruitment

Sampling technique

The PEDAL study includes a target and comparison groups. The variables that this study sets out to explore (ie, safety, effectiveness, tolerability and patients' unmet needs) will be better comprehended by including groups of participants on other regimens to allow for comparison. However, and in light of our iterative approach, the inclusion of comparison groups will be evaluated as the study progresses. For example, if the CDA data reveal unique findings for the two and three drug regimens, then we will continue the study with a comparison group consisting of people on both two and three drug regimens. If the data do not reveal unique findings within the dual-drug regimen comparison group, then the control population for the FGDs and IDIs will be modified to only include patients on three-drug regimens excluding those on alternative dual-drug regimens.

We will use purposive sampling to recruit a diverse population in terms of age, gender, socioeconomic status, ART, treatment duration and number of previous ART regimes. Particular attention will be placed on recruiting participants from underrepresented groups (eg, age≥70 years; women; people with history of challenges to adherence and people with comorbidities). In the event of an insufficient sample recruited via a purposive sampling strategy, we will use snowball sampling where participants recruit future subjects from their networks (providing they meet the inclusion criteria).

Participants will be recruited through various methods. First, the research team will screen the clinical database to identify individuals to be recruited during clinical sessions. Clinical research nurses will support participant identification and screening to check patient eligibility with extra emphasis on identifying unrepresented groups. They will provide patients with a study information sheet and a researcher will approach the patients to obtain verbal consent should they want to learn more. Additionally, participants will be recruited through peer support groups, women's groups, online groups, flyers emailed and handed directly to patients by doctors and to be circulated among consultants, nurses and by the Research Assistant in the clinic. Doctors, consultants and nurses will help ensure unrepresented groups receive study information. Patients interested in taking part in the study will be offered to discuss the project further with a team member acting as a representative of PLWH. We expect that being able to speak with someone they can identify with will reduce hesitation to participate, build confidence and increase motivation to stay engaged.

Participation will be in-person or online depending on the COVID-19 guidance and participants' preferences. Participants will be offered up to £30 in vouchers to compensate for their time. They will receive £10 for participation in one method; £20 for participation in two methods and £30 for participation in all three methods. Additionally, those based in Brighton and Hove will be reimbursed for travel costs.

Sample size

Out of a total HIV cohort composed by more than 2000 patients at the Royal Sussex County Hospital (RSCH), there are currently 87 patients on the dual drug regimen DTG/3TC. We will approach all 87 patients to participate in the study; however, based on previous study recruitment at our centre, we anticipate about 20% of those approached to consent. During the CDA phase, we will recruit a minimum of 8 and up to 40 participants from the target population and 80–116 participants from the comparison population for a sample range of 80–120 participants. On completion of the CDA phase, we will conduct 1–2 FGDs with each group, with each consisting of 6–10 people. Finallly, we aim to conduct 6–12 IDIs with patients from each group. Should we fail to recruit the minimum number of participants, other HIV care providers of the Kent, Surrey, Sussex NHS Clinical Research Network will be approach and invited to be part of the study.

The sample size used in qualitative research methods is often smaller than in quantitative research. This is because qualitative research is mostly concerned with gaining an in-depth understanding of a phenomenon and is focused on meaning. IDI is not necessarily concerned with making generalisations to a larger population and do not tend to rely on hypothesis testing but is rather a more inductive process. As such, the aim of FGD and IDI data is to create analytical, demographic and ethnographic categories to analyse relationships between categories while attending to the lived experience of participants.[27 28]

We will follow the principle of data saturation, when the data collection process no longer offers any new or relevant data. Conducting interviews, scholars have found that data saturation often occurs within the first twelve interviews while meta-themes might appear after six interviews.[29] If we determine that saturation has not been achieved in any method, then the time period for recruitment will be extended.

Inclusion and exclusion criteria

Adult PLWH (age≥18 years) will be invited to participate if they have capacity to consent, receive HIV care at the RSCH HIV Department in Brighton, and are on one of the following therapies:

1. Target population: DTG/3TC
2. Comparison population
   a. *Groups on dual-drug therapies:*
      1. DTG/RPV
      2. DRV/r or DRV/c + 3TC
      3. DRV/r or DRV/c + RAL
   b. *Groups on triple-drug regimens:*
      1. 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) + 1 InSTI.
      2. 2 NRTIs + 1 non-nucleoside reverse transcriptase inhibitor (NNRTI).
      3. 2 NRTIs + boosted protease inhibitor (PI/b)

Patients taking DTG/3TC with a history of virological failure or suspected resistance to 3TC or DTG will be excluded. Patients not fitting the inclusion criteria including those taking other drug combinations due to complex HIV resistance patterns, ART naïve or individuals declining ART will be excluded. Patients without access to the technology to take part online will be given the option to participate in person (depending on COVID-19 guidance). If this is not possible, they will be excluded.

No minimum of treatment duration will be required.

Data collection

We will employ three main methods: CDA, FGDs and IDIs. Participants will be given the option to take part online or in person. Online participants will be able to join via Microsoft Teams, Zoom or Skype from a location of their choosing. In-person participants will attend a quiet room at the Clinical Research Facility at the University Hospitals Sussex or at The Sussex Beacon. During FGDs, those

attending physically will be informed that everything discussed within the room should remain confidential and that identities cannot be disclosed outside.

Cultural domain analysis

CDA is an approach derived from cognitive anthropology to describe the contents, structure and distribution of knowledge in organised spheres of experience, or cultural domains.[30] The goal is to understand how people in different cultures (or subcultures) interpret the content of domains differently.[31] Asking participants to discuss positive and negative factors related to their treatment, CDA will focus specifically on exploring the *unmet needs* of patients on dual-drug or triple-drug therapy.

When facilitating CDA sessions, we will employ three tools: free listing, pilesorts and rankings. Free listing is a simple method where participants are asked to list all they know about a particular topic to get them to mention as many items as they can in a domain. After completing the free listing exercise, we will introduce the pilesort task to elicit judgements of similarity among the items shared during the free listing question.[31] The final section will ask participants to rank order the positive/negative factors that most/least meet their treatment needs and support their quality of life while undergoing treatment.

When CDA is conducted in-person, we will ask participants to write their answers on notecards and to use these cards to complete the pilesort and ranking tasks. When conducted online, we will use Padlet®, a real-time participatory online platform where users can share and organise content to virtual boards called 'padlets'. At the start of each session, participants will receive a unique and confidential link to a new Padlet® page. The page will be linked to the researchers' professional account and no personal data will be linked to the participant. Both the researcher and the participant will log into the same Padlet® page at the same time. This will allow the researchers to observe the participant list, sort and rank their domains in real time. At the end of the session, the researcher will export the Padlet® board as an image and save it in a secure, password-protected location for analysis.

Focus group discussions

After completing the CDA sessions, we will conduct data analysis in line with our iterative approach. We will then hold 1–2 FGDs with each group, in-person or online. In the FGDs with patients on DTG/3TC, we will elicit experiences on the treatment and perceptions before switching to it. In the FGDs with patients on other dual and triple-drug therapy, we will explore perceptions of DTG/3TC, of ART, and of the future of HIV care and treatment generally.

Each FGD will have a moderator and a facilitator. Due to potential hesitancy to disclose their status to others, online participants will be able to choose if they want to have their video on or off and if they would like to use a pseudonym.

In-depth interviews

Following completion of the FGDs, the research team will analyse the data to refine interview questions. After this, we will conduct 6–12 IDIs with participants on DTG/3TC to elicit narratives and treatment histories of the regimen. IDIs with the target population will allow participants to share specific experiences, fears, hopes, concerns and unexpected outcomes of the therapy. Interview data will be analysed according to the variables of *safety*, *tolerability* and *effectiveness* to provide case studies of patients' experiences. We will also conduct 6–12 IDIs with participants on alternative dual therapy treatments, and 6–12 IDIs with participants on triple-drug therapy regimens. This will allow us to learn about potential misconceptions, misunderstandings, rumours and knowledge gaps around DTG/3TC from patients on alternative therapies.

All interview guides can be found in the online supplemental files 1-3.

Data analysis

Quantitative data emerging through CDA will be analysed through ANTHROPAC®, a software used to collect and analyse data on cultural domains. We will conduct proximity analysis to compute measures of similarity and difference between respondents on DTG/3TC against dual-drug therapy and triple-drug therapy. Audio-recordings from FGDs and interviews will be transcribed and coded on NVIVO®.

Data will be analysed using ATA to identify implicit and explicit ideas. Defined as 'a method for identifying, analysing and reporting patterns (themes) within data',[32] it has been used in public health research to address issues that are practical or applied in nature.[33] In ATA, the researcher identifies key themes that are transformed into codes. Following an analysis of each group, a second stage analysis will be conducted to compare and contrast findings across groups. The analysis will seek out consensus, disagreement and inconsistency among participants.

Ethics and dissemination

Ethical considerations

When participants are identified by members of the healthcare team, they will seek oral consent to contact them with further information about the study. Once participants have orally agreed to participate in an eligibility screening or for us to share further information about the study, we will begin the process of obtaining informed consent. We will give the participants an information sheet and consent form, which they will be asked to return signed and dated before proceeding to the next phase. Prior to any CDA, FGDs and IDIs the researcher will again seek oral consent to ensure the participant has read and understood the information sheet and consent form.

Participants will be invited to join all components of the research. However, they may choose to take part only in the first method, the first and second method or all three methods. If participants take part in more than one

method, both informed written and oral consent will be taken prior to participating in each of the sessions. Ethical approval has been obtained from the Health Research Authority Research Ethics Committee (REC reference: 21/NW/0070).

Data protection and patient confidentiality

All investigators will comply with the requirements of the Data Protection Act (2018) with regard to collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Participants' information will be replaced by an unrelated unique sequence of characters to guarantee anonymisation. A reconciliation list will be created and stored in a locked cabinet with the study protocol at the Clinical Research Facility at the RSCH, whereas anonymised data collected via the audio-recording of the FGDs and the IDIs, and the images from the CDA will be saved in a folder on the University of Brighton OneDrive, which only the research team will have access to.

Output and dissemination

Study findings will be disseminated via journal articles, conference papers and discussions through public engagement events with BSMS and the Sussex Beacon including recommendations to be used in practice. These activities will contribute to informing the future of HIV treatment by providing evidence of patients' perceptions and experiences of dual-drug regimens. Ultimately, we expect to improve doctor and patient communication by identifying patient fears, worries, misconceptions, and general concerns of their drug regimen.

DISCUSSION

Despite the existence of clinical evidence of the safety, effectiveness and tolerability of dual-drug regimens,[8] there is currently limited insight into patient experiences and perceptions of dual-drug combinations, including DTG/3TC. Our study will therefore contribute to knowledge by exploring patients' experiences and perceptions of dual-drug regimens, including potentially unmet treatment needs and reported outcomes for those on this drug combination. Through the CMA approach, we will be able to better understand human psychobiological systems, patients' experiential responses to illness, their support networks and physician–patient interactions in relation to the DTG/3TC treatment regimen and future direction of dual-drug HIV treatment. Having first-hand patient knowledge of DTG/3TC means ViiV Healthcare can improve their communication of the drug and that healthcare providers and support networks can improve communication with patients about their treatment and the future of HIV treatment.

Limitations

The selected target and comparison populations involve a potential limitation because of the lack of engagement with other groups excluded from the study (ie, those taking different drug combinations due to complex HIV resistance patterns, ART naïve or declining ART). Moreover, the Brighton cohort is largely composed of men who have sex with men, hence might not be fully representative of other contexts in the UK. All efforts will be in place to recruit under-represented groups: for example, to ensure an adequate enrolment of women, we will target a dedicated service for women living with HIV at the Lawson Unit (the Sunflower Clinic). No formal matching of patients between groups will take place, and this might generate unbalances that could potentially influence the findings. All efforts will be in place to balance the groups according to age, gender, and ethnic background to mitigate this risk.

The current COVID-19 pandemic has been limiting face-to-face interactions in routine clinical practice in the attempt to contain the spread of the virus. We have overcome this barrier by designing online digital methods, however potential participants who do not have access to the required technology to participate and that cannot or do not wish to take part in person will be excluded. Despite the potential limitations of digital methods for less tech-savvy participants, this approach presents benefits such as increased anonymity due to the option to turn one's camera off or use pseudonyms. Additionally, accessing the online venue might be less of a barrier to participation than finding time to travel to the research location.[34]

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Contributors GV is the chief and principal investigator of the study, he conceptualised the study and wrote the protocol with CA; DGR is a research assistant, he converted the protocol into its publishable format and coauthored the protocol; DF and AC are coinvestigators and coauthored the protocol; CA is the coprincipal investigator of the study, she conceptualised the study and wrote the protocol with GV. All authors supported the development and critical review of the protocol and of this manuscript.

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Competing interests GV declares a research grant from ViiV Healthcare to his Institution to run the study presented in the manuscript; AC declares direct payments from Gilead Sciences, ViiV Healthcare, MSD, Theratechnologies for participation in advisory boards; a sponsorship from Gilead Sciences for conference attendance; research grants from Gilead Sciences, ViiV Healthcare, MSD to her Institution for running clinical trials. All the other authors have no competing interests to declare.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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