Qualitative Protocol Development Tool

FULL/LONG TITLE OF THE STUDY

Lamivudine (3TC) plus dolutegravir (DTG) dual therapy: a study on patients' experiences and perceptions

SHORT STUDY TITLE / ACRONYM

Patients' experiences and perceptions of 3TC/DTG dual therapy (the PEDAL Study)

PROTOCOL VERSION NUMBER AND DATE

Version 2.0 03/12/2020

RESEARCH REFERENCE NUMBERS

IRAS Number:	**286277**
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

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

For and on behalf of the Study Sponsor:

Signature:

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Date:

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Name (please print):

.....

Position:

.....

Chief Investigator:

Date: 04/06/2021

Signature:

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Committees	Not applicable

STUDY SUMMARY

Study Title	Lamivudine (3TC) plus dolutegravir (DTG) dual therapy: a study on patients' experiences and perceptions
Internal ref. no. (or short title)	Patients' experiences and perceptions of DTG/3TC dual therapy (the PEDAL Study)
Study Design	Qualitative study
Study Participants	People living with HIV receiving HIV care at the Lawson Unit and the Clinical Research Facility at the University Hospitals Sussex NHS Foundation Trust, Brighton, United Kingdom; Target population: patients on DTG/3TC Control population: patients on other dual and triple therapy regimens
Planned Size of Sample (if applicable)	• Cultural Domain Analysis: at least 80 and up to a maximum of 120 participants • Focus Group Discussions: at least 18 and up to a maximum of 60 participants • In-depth Interviews: at least 18 and up to a maximum of 36 participants TOTAL: 116-216 participants
Follow up duration (if applicable)	Not applicable
Planned Study Period	April 2021 - September 2022
Research Question/Aim(s)	Research questions: What are patients' experiences and perceptions of the safety, effectiveness, and tolerability of the 2-drug regimen DTG/3TC? What are the unmet needs of patients undergoing the 2-drug regimen? Aim: To explore patients' perceptions and experiences of the 2-drug treatment regimen DTG/3TC, including potentially unmet treatment needs. Objectives: • To investigate patients' perceptions and experiences on the safety, effectiveness, tolerability, and unmet needs of the DTG/3TC 2-drug regimen • To conduct comparative analysis of the safety, effectiveness, tolerability, and unmet needs between patients on the DTG/3TC 2-drug regimen and patients on other two-drug and three-drug combinations • To provide recommendations that improve doctor-patient communication, knowledge and understanding of treatment plan, and additional care that ought to be considered in patient-centred, holistic care plans

FUNDING AND SUPPORT IN KIND

The research described in the protocol is being funded by ViiV Healthcare.

ROLE OF STUDY SPONSOR AND FUNDER

The role of the study sponsor is to provide institutional approval to guarantee the study is aligned with research ethics. The study sponsor was not involved in the development of the study.

The sponsor is the employer of Dr Giovanni Villa, Chief Investigator. The sponsor has had and will have no input or influence in study design, conduct, data analysis and interpretation, manuscript writing and dissemination of results.

The Funder is ViiV Healthcare. Quarterly reports will be provided to the funder. The funder will review all material for publication or presentation concerning the research activities of the award. The funder's role in the study design is limited to providing reviewer comments and suggestions. They have no role or responsibility in conducting the study, data analysis and interpretation, manuscript writing, and dissemination of results. The funder does not control the final decision regarding any of these aspects of the study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The study includes one patient representative whose roles are described according to the INVO Patient and Public Involvement briefing. The patient representative helped adapt in-person methods to online by taking part in a User Acceptance Study and providing feedback. They reviewed and commented on the study protocol. They will help recruit participants from their professional networks. They will facilitate and support public engagement activities at the end of the study. Their role will be independent from the Sponsor and Investigators as they represent patients and the Sussex Beacon.

PROTOCOL CONTRIBUTORS

- Ackley, Villa, Clarke (Authors)
- ViiV Healthcare (Funder)
- University of Sussex (Sponsor)
- Joint Clinical Research Office (JCRO) – University of Sussex
- Patient representatives and co-author: David Fray

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- Dr Rayner Tan
  National University of Singapore, Public Health
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Internal reviewers:

- Professor Melanie Newport

  BSMS, Global Health and Infection
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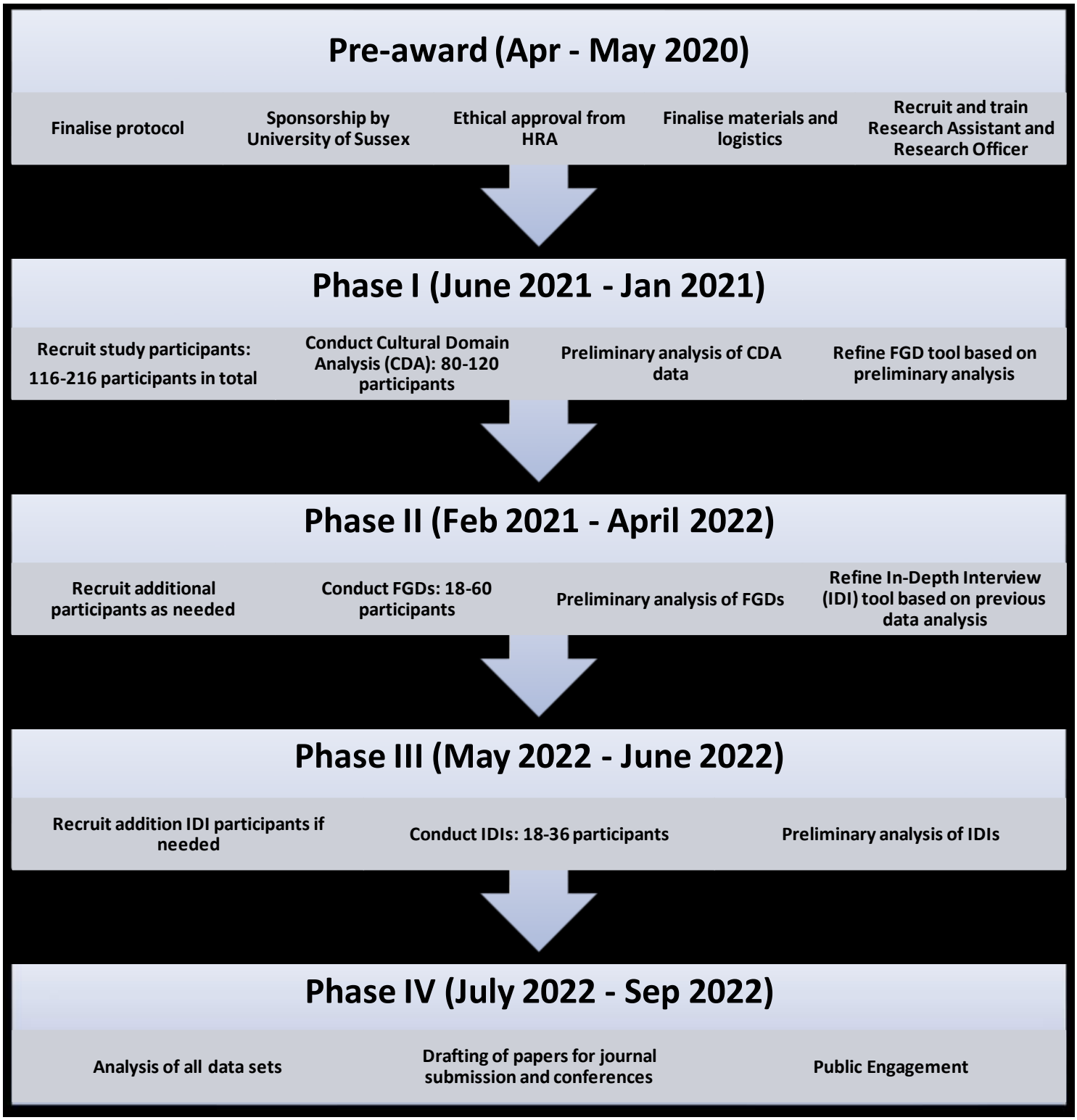
Patient representatives participated in the User Acceptance Study conducted prior to the submission of this protocol to inform how to adapt Cultural Domain Analysis from in-person to online. Therefore, patient representatives have been involved in determining appropriate methods for the study. They will also participate in the dissemination of results through community gatherings in Brighton and at the Brighton and Sussex Medical School.

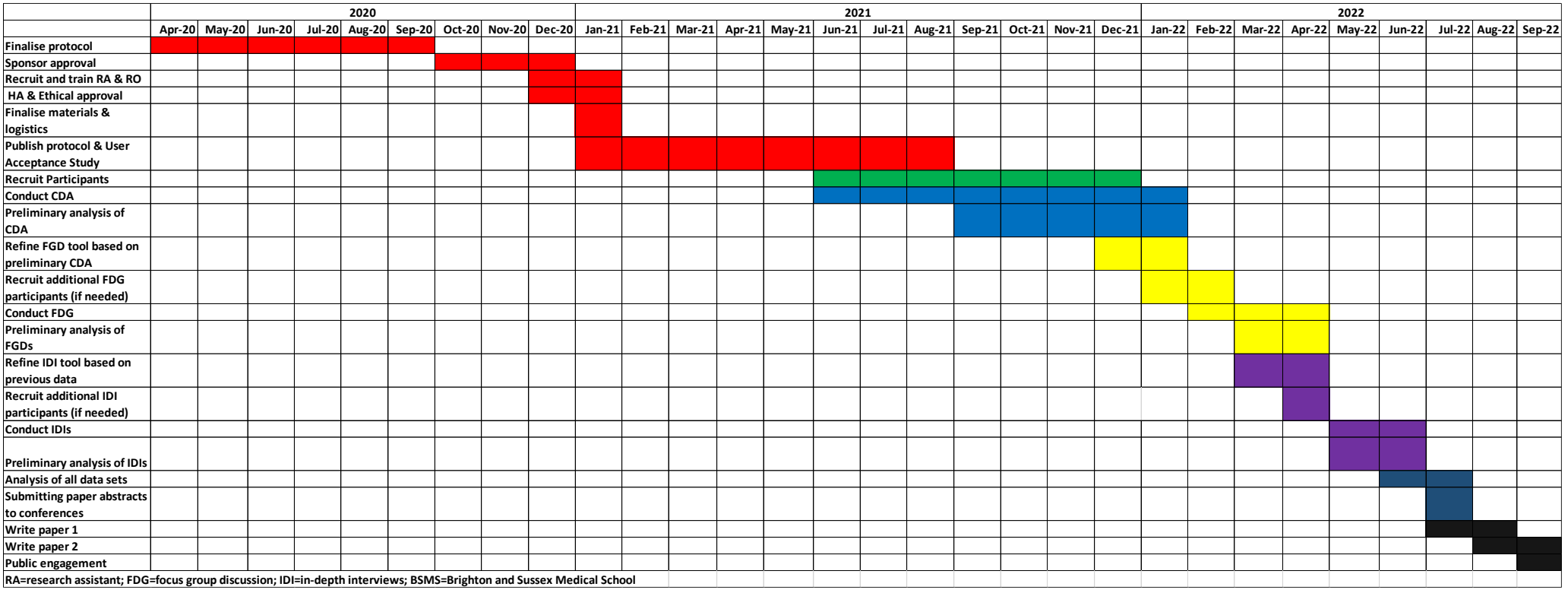
KEY WORDS: Qualitative Research; Perceptions and Experiences; dolutegravir/lamivudine; Tolerability; Safety; Efficacy; Unmet Patient Needs

STUDY FLOW CHART



PATIENT ACTIVITY PATHWAY

STUDY TIMELINE



STUDY PROTOCOL

Lamivudine (3TC) plus dolutegravir (DTG) dual therapy: a study on patients' experiences and perceptions

1 BACKGROUND

Literature review

Dolutegravir (DTG), an integrase strand inhibitor (InSTI), is currently recommended for both treatment initiation and second/third line therapy for HIV-positive individuals, in combination with either tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), tenofovir alafenamide (TAF)/FTC or abacavir/lamivudine (ABC/3TC).[1–3] 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,[4] and the European guidelines have introduced this option among recommended first-line regimens.[2] Based on the results of the ASPIRE,[5] LAMIDOL,[6] and, ultimately, TANGO studies,[7] the dual combination DTG/3TC has also proven to be a safe and effective option for treatment simplification of HIV-experienced suppressed individuals on triple therapy.

Dual-drug combinations offer the advantage of a reduced exposure to antiretroviral agents, hence a potential reduction in drug-associated side effects in the long-term.[8] In addition to DTG/3TC, the SWORD-1 and SWORD-2 trials have demonstrated the non-inferiority of the dual-drug combination DTG/rilpivirine (RPV) for treatment simplification,[9] and a novel, long-acting, molecule of the InSTI class, cabotegravir, has proven non-inferior, when co-administered with RPV intramuscularly every four weeks, to triple class regimens, in both the FLAIR and ATLAS trials.[10] Regimens using fewer drugs are undoubtedly destined to represent a larger share of the treatment options for people living with HIV in the near future, hence research on their effectiveness and tolerability is crucial.

Although there is clinical evidence of the safety, effectiveness, and tolerability of dual-therapy regimens,[8] there is limited insight into patient experiences and perceptions of dual-drug combinations, including the DTG/3TC regimen. In our study, we intend to conduct a comparative qualitative analysis to explore patients' experiences and perceptions of dual-therapy regimens, including potentially unmet treatment needs and reported outcomes for those already on this drug combination. This study would be the first of its kind to provide patient-centred insight into this specific treatment combination and to provide recommendations for improved clinical care.

Study description

We propose a three-phase comparative study with a control population (i.e., HIV-positive individuals on other dual therapy regimens and triple ART) and the target population (i.e., HIV-positive individuals on dual DTG/3TC regimen) (Figure 1). The control population will include a group on dual regimens other than DTG/3TC and a group on triple therapy. In the control group of patients receiving dual therapies, we will include patients (i) on Juluca (DTG/rilpivirine[RPV]), (ii) on boosted darunavir plus lamivudine (DRV/r or DRV/c + 3TC), and (iii) on boosted darunavir plus raltegravir (DRV/r or DRV/c + RAL). The target population will include patients on DTG/3TC. The addition of the control group of patients on other dual therapies will allow us to tease out the particular characteristics of the dual DTG/3TC beyond the mere reduction of molecules employed for the treatment.

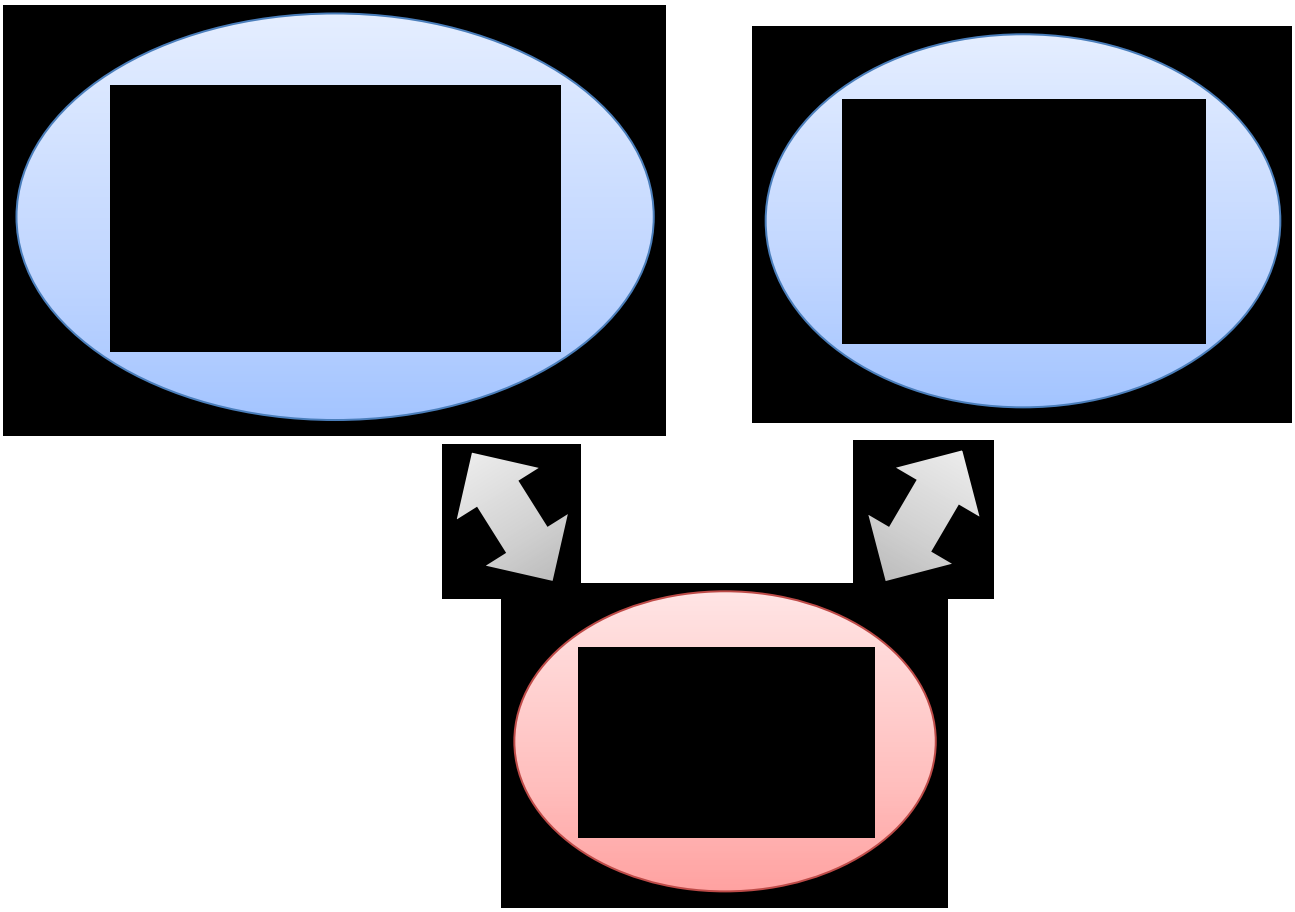


Figure 1. Target and control populations. The arrows indicate that the comparative analysis will take place between the target population and the two control groups separately.

We suggest that a comparative study including the target and control populations will allow us to better understand patient perceptions and needs as related to the variables of (i) safety, (ii) effectiveness, (iii) tolerability, and (iv) unmet needs. This is because DTG/3TC will not be experienced and perceived in isolation from patient's previous drug regimens or from other patients on different drug regimens. When a participant on DTG/3TC describes their experiences and perceptions, they will be making a comparison to a 'time before' or to 'an other'. For example, we anticipate patients to describe current experiences of DTG/3TC effectiveness in comparison to a time they were on another drug regimen or in comparison to a friend/known person on another drug regimen (e.g. 'DTG/3TC is more effective than my previous treatment' or 'DTG/3TC seems to be less tolerable because my friend is on a different regimen and has fewer side-effects'). This supports the need to explore other drug regimens through a control group so that comparisons that arise in the data will have a reference point rooted in data. In short, if a patient says 'DTG/3TC is safer than my previous treatment' we can understand not only experiences on DTG/3TC, but also how it compares to other treatments.

Additionally, the subjective nature of these variables means that each person will have a different understanding, meaning, perception, and experience of the study variables. ViiV Healthcare, the researchers, and health care providers will have one, or more, way of defining the variables, but there is added value in exploring what they mean to patients. By widening our participant population to not just include the target population, but to also include the control groups we will gain a more in-depth understanding of what these variables mean to patients.

This will ensure conceptual and operational alignment of the variables between patients and researchers. So, when we report findings from the study on safety or tolerability, there is conceptual and linguistic alignment.

The 'phases' refer to the order in which specific methods will be deployed and findings preliminarily analysed. In Phase I we will deploy Cultural Domain Analysis (CDA), a type of structured interview aimed at understanding how people in a group think about lists of things that somehow go together. CDA will help us to better understand patient unmet needs. After data collection we will conduct preliminary analysis to refine and improve our Focus Group Discussion (FGD) questions and approach. In Phase II we will conduct FGDs to gain deeper knowledge of patient unmet needs and to begin exploring the variables safety, efficacy, and tolerability. We will conduct preliminary analysis of the FGDs to refine the questions and approach we take in In-Depth Interviews (IDI). In Phase III we will conduct IDIs to gain expert knowledge and understanding of the variables safety, efficacy, and tolerability. We will conduct preliminary analysis of the data. Finally, we will analyse all data sets, prepare journal articles, conference papers, and share findings through public engagement with both the Brighton and Sussex Medical School and the Sussex Beacon.

We will ask the control population to draw on their knowledge of the DTG/3TC regimen, and the target population to share their experiences on DTG/3TC; both in relation to the above-mentioned variables. By asking the control population about the DTG/3TC regimen (as opposed to their current care plan) we will illuminate potential gaps in knowledge and understanding about the DTG/3TC regimen, as well as potential misconceptions among HIV patients in treatment about the 2-drug therapy.

We will also ask the control population about their current dual and triple therapy regimens and the target population about their previous experiences on triple therapy or alternative dual therapy combinations before switching to the DTG/3TC regimen; both in relation to the above-mentioned variables. By including exploration of different treatments, we will gain understanding of whether patients perceive the new regimen to be safer, effective, and more tolerable, as well as if they feel previously unmet needs are now met on the new treatment plan. We can also gauge the potential interest and/or concern/worry/fear that patients on triple and alternative dual therapies may feel about the future direction of HIV treatment.

This data will enable us to provide recommendations for improved doctor-patient communication and health education about the 2-drug and DTG/3TC regimen. It may also allow us to identify psycho-social concerns that support teams should be aware of or anticipate as patient treatment plans change.

Study population

The Lawson Unit and the Clinical Research Facility at the University Hospitals Sussex NHS Foundation Trust provide HIV care for a population of around 2,500 individuals living with HIV. The HIV cohort is composed predominantly by men (~85%). In 2018, prevalence of HIV infection in the general population in Brighton and Hove exceeded 5 per 1,000 in the population aged 15 to 59 years in some areas, representing one of the highest figure of the United Kingdom; 50% of PLWHIV in Brighton and Hove are over 50 years old, so the prevalence may not include under 59's.[11,12] Brighton and Hove was the first city in the UK to achieve "Fast Track City" status in 2016; the most recent data from Brighton show that 93% of people living with HIV know their status, 99% of those are on treatment and 98% of those on treatment have an undetectable viral load.[13]

People living with HIV still experience stigma and we acknowledge that members of the study population may experience it themselves. Stigma may be experienced in the forms of self-stigma, perceived and/or anticipated stigmas. Self-stigma is 'a stigmatized group member's own adoption of negative societal beliefs and feelings, as well as the social devaluation, associated with their stigmatized status'.[14] Perceived stigma is the 'perceptions about how stigmatized groups are treated in a given context' and anticipated stigma is the 'expectations of bias

being perpetrated by others if their health condition becomes known'.[14] The drivers of stigma might be rooted in fear, judgement, blame, stereotypes and prejudice while the facilitators might be social and gender norms, health policy, and the legal environment. Additionally, experiences of stigma can vary from demographic and length of time since diagnosis. We acknowledge that participants in this study as well as those who do not participate may experience HIV-related stigma, therefore we have included a patient representative, Mr. David Fray, and several independent organisations to support participants who may want to talk about any questions or issues that arise before the study, while taking part in the study, and upon completion of the study. We will also hold a public engagement event in partnerships with the Sussex Beacon in Brighton so that the findings of the study can be disseminated and discussed amongst the HIV community with the hope of improving patient care and experiences.

2 RATIONALE

In this qualitative study we propose to investigate if patients perceive and experience the DTG/3TC 2-drug regimen as beneficial according to the variables of safety, effectiveness, tolerability, and unmet needs, including comparison with other 2 and 3-drug regimens. In other words, rather than measuring viral load to determine 'benefit' we are asking patients to tell us of their experiences and perceptions of DTG/3TC to determine 'benefit'. It is possible some patients might not perceive their experiences as positive and thus feel they have not benefitted from the drug regime, regardless of their viral load or side effects.

We argue that this is valuable information for ViiV Healthcare and the future of HIV treatment more generally because patients not only need their viral loads to be managed and ideally supressed, but they also need to feel that they are benefiting from whatever drug regime they are on. The risk is that if patients do not feel they are benefitting, then they might not adhere to treatment regimens or they might request healthcare providers to administer different treatment regimes, ones they perceive more positively.

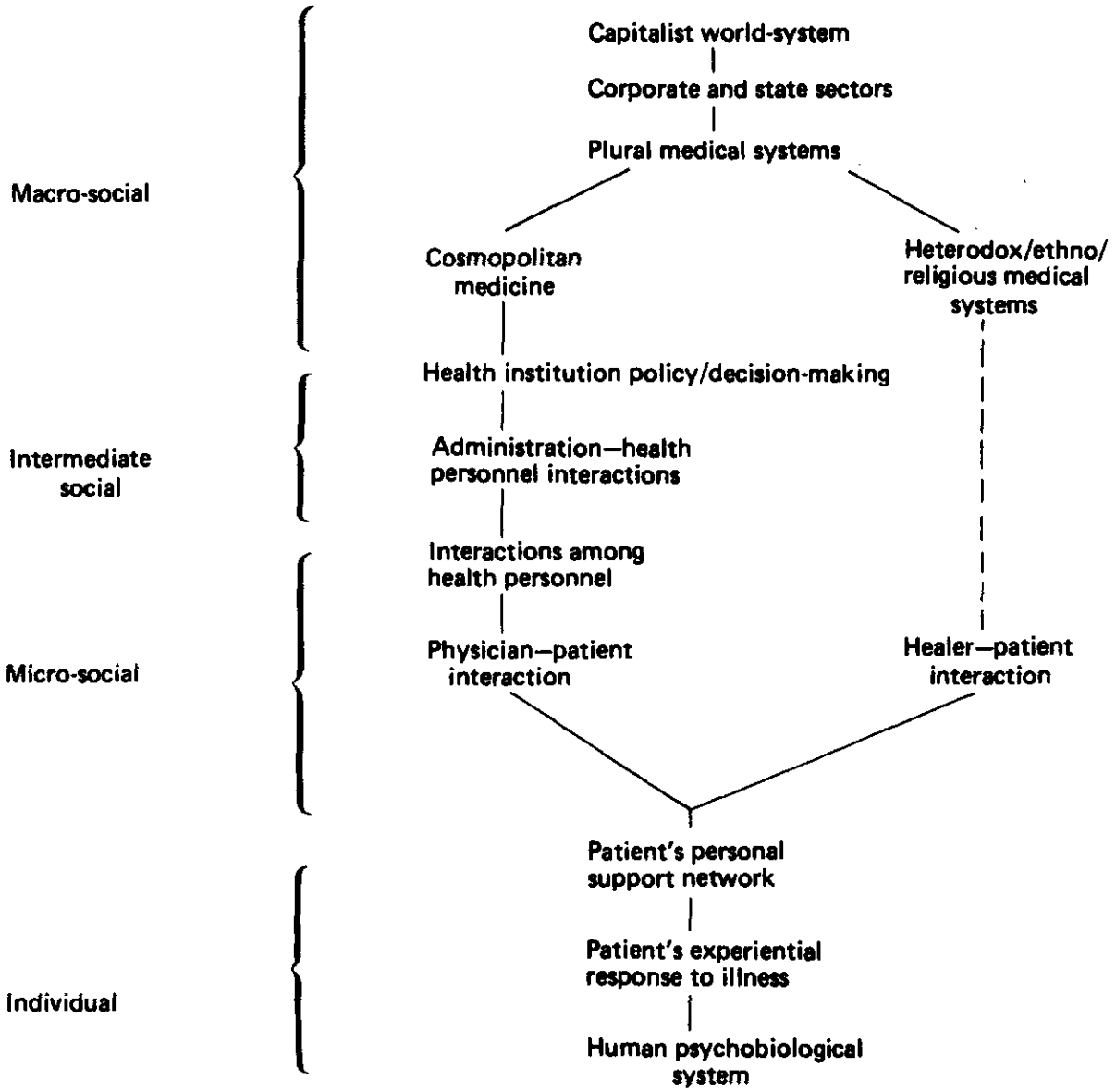
We suggest the primary objective is to investigate patients' perceptions and experiences on the safety, effectiveness, tolerability, and unmet needs of the DTG/3TC 2-drug regimen. The secondary objective is to conduct comparative analysis of the safety, effectiveness, tolerability, and unmet needs between patients on the DTG/3TC 2-drug regimen and patients on other two-drug and three-drug combinations. The study aims to analyse and disseminate the data collected, and to provide recommendations that improve doctor-patient communication, knowledge and understanding of treatment plan, and additional care that ought to be considered in patient-centred, holistic care plans.

3 THEORETICAL FRAMEWORK

The theoretical framework that informs this study is rooted in the branch of medical anthropology called Critical Medical Anthropology (CMA). We apply this theoretical approach to the micro-social and individual levels of analysis in the health care system [15] by studying patients' experiences and perceptions of the DTG/3TC regimen (see Figure 1). Through this approach we can better understand the human psychobiological system (psychological and biological connection), patient's experiential responses to illness and their personal support networks, and physician patient interactions all in relation to the DTG/3TC treatment regimen and future direction of 2-drug HIV treatment. Patients understand, perceive, and experience the DTG/3TC regimen within the social, political, and economic systems that structure our world. Although this study does not focus on the political and economic world order, we feel it is important to contextualise the study of health and illness in such a theoretical framework. In what follows we justify CMA as a guiding theoretical framework and describe how CMA has been integral to the study of HIV/AIDS. We describe 'the social' part of this study by focusing on the

'social' lives of medicines where medicines are objects that have the power to influence social and biopsychological relations at the individual and micro-social levels. We take the DTG/3TC drug regimen to be more than a series of tablets consumed to control viral load. We take the tablets to also be social objects that we follow through the treatment process in an effort to understand the individual and inter-personal interactions that comprise the ways that patients perceive and experience tolerability, effectiveness, and safety of the DTG/3TC regimen.

Figure 1: Levels of health care systems



Critical Medical Anthropology

Critical medical anthropology (CMA) is a branch of medical anthropology that was coined in 1982 by Baer and Singer in a paper presented at the American Anthropological Association meeting[16]. CMA is a theoretical perspective that understands health issues within the political and economic contexts that 'pattern human relationships, shape social behaviours, condition collective experiences, reorder local ecologies, and situate cultural meanings' (ibid. pg. 43). 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 health care resources;' and (3) the 'opportunity for health-promoting interventions' (pgs. 10-11).[17] 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.[18]

CMA differs from the popular public health theory social determinants of health (SDH). In 2004, the WHO Commission on Macroeconomics and Health created the Commission on Social Determinants of Health, however the SDH 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.[16] In contrast, CMA not only identifies such factors, but also attempts to understand the broader context and causes of inequality, poverty, unemployment, etc. CMA reaches beyond identifying factors like sexual behaviour as a determinant of health to understanding what shapes those behaviours in the first place. The social determinants of health approach fails to consider the capitalist world system in which the political, economic, and social processes that shape the quality of determinants are located.[19] We 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. 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.

CMA draws on the theoretical assumptions of critical theory, a social theory oriented toward critiquing and changing society as a whole while 'decreasing domination and increasing freedom in all their forms'.[20] It is built on the scientific method (namely empiricism and objectivity), while recognising that reality is conditioned by social circumstance and open to critical examination and debate. Science emerged and operates within a given set of cultural circumstances that are influenced by the worldview and values particular to those circumstances.[16] The scientific method demands open and constant critique and self-examination (ibid.), which drives the way we apply CMA in the study design (as an iterative process).

Critical Medical Anthropology and HIV/AIDS

The anthropological study of HIV/AIDS drastically shifted in the mid-1990s when Merrill Singer applied the theoretical framework of CMA[16,21] to the study of HIV/AIDS. In his article 'AIDS and the Health Crisis of the U.S. Urban Poor; The Perspective of Critical Medical Anthropology,' Singer suggests that the social identity of HIV/AIDS in the US has been shaped by social relations across class, race, gender, and sexual orientation, as well as by public health categories of disease. To study the social identity of AIDS is to study the human biocultural experience, and how the disease affects the ways we live and organize society.[22–24] The disciplines we deploy to study this new reality are also affected and anthropologists and social scientists should 'be professionally suspicious of our categories and models; we should be aware of their historical and cultural contingencies'.[24] Thus, there was a shift in anthropological and social scientific approaches to HIV/AIDS where the disease was re-situated in a broader perspective that included the health and social conditions that structure it.[22]

Singer does not examine HIV/AIDS 'in isolation as a new epidemic with unique features,' (pg. 993)[22] rather he examines it in terms of a broader health crisis. His early work on HIV is still relevant today due to the concept of syndemics as a tool to understand the 'set of synergistic or intertwined and mutual enhancing health and social problems facing the urban poor' (ibid.). Syndemics examines co-deleterious disease interactions and the political, economic, and social contexts in which they are situated. He argues that urban minority populations

suffer disproportionately from underlying conditions (hypertension, cirrhosis, diabetes), preventable diseases (STDs, HIV TB), and substance abuse. The diseases and conditions that comprise an urban syndemic are interconnected. For example, 'poverty contributes to poor nutrition and susceptibility to infection'; 'poor nutrition, chronic stress, and prior disease' result in a weakened 'immune system thus increasing susceptibility to new infection'; and, many 'socio-economic problems and stressors increase the likelihood of substance abuse and exposure to HIV' (ibid). In applying sydemics Singer challenges (at the time) taken for granted conceptual categories that wondered if there was something biological or in the social behaviour of gay or bisexual men and IV drug users that was causing this new disease. However, providing clearly defined and bounded descriptors of homosexuality or IV drug use to identify people at special risk or in need of special prevention efforts proved complicated and to have many unintended consequences. These consequences include the perpetuation of misunderstandings of who is at risk and how, mistargeting health education, stigmatization, dividing communities and reinforcing social divisions, spreading the disease, and concentrating public health resources only on AIDS while ignoring the social and syndemic nature of AIDS [22]. Singer illustrates that understanding the social construction of AIDS is critical to 'fighting' it (ibid.). This approached, coined by Singer, has shaped much of medical anthropology and is taking hold in public and global health.

The CMA perspective argues that HIV need not be seen as having an existence independent from human activity and culture, including political economy, even if it is assumed to be a 'part of nature' because 'nature need not be understood from an ahistoric naturalistic perspective' [22]. Singer has shown us that the study of disease must include a wider exploration of the systemic structures in which it is located, the co-deleterious conditions with which it interacts, and the social worlds it creates and moves within. This perspective has now been widely adopted and applied to not only the study of HIV/AIDS, but within entire disciplines like anthropology, the social sciences, and public health. We use this theoretical perspective to inform how we study HIV/AIDS more broadly, and to how we explore patients' perceptions and experiences on and of DTG/3TC. We do this by suggesting that not only does disease have a social life, but so do the medicines used to treat them.

Social lives of medicines

In this research we take medicines 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 [25]. Following [26] we are concerned with the social uses and consequences of medicines, specifically DTG/3TC. Medicines have relationships 'with people and between people' (ibid. 14) and are the 'most personal of material objects' (ibid. 3) with the power 'to transform bodies' (ibid. 5). They 'can be simultaneously noxious and beneficial' (ibid. 6). This does not mean that we overlook or ignore the therapeutic functions medicines have but building on [27] we intend to draw attention to the aspects of medicines that tend to be overlooked. This study allows us to pay attention to the non-medical meanings and effects of medicines by understanding how DTG/3TC means different things and serves different interests to different people in different situations (ibid. 4).

In undertaking a study of patient perceptions and experiences of DTG/3TC we will explore patients' own rationalities for use of medicines; for example, patients might skip prescribed doses at the weekend when they intend to take 'club drugs' that negatively interact with their medicine. This might impact how patients perceive or experience the tolerability of a drug- not just in terms of tolerability of side-effects but also tolerability in regard to lifestyle. We 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 health care professionals and patients on a case by case basis [28]. Additionally, safety of DTG/3TC must

be understood in relation to patient vulnerability, particularly in relation to their own situation. What we hope to show is that to truly explore the study variables (tolerability, efficacy, and safety) we must take medicines to be social objects while also locating the study of HIV in broader structures that guide our daily lives.

In conclusion, we suggest that in adopting this theoretical framework we can best understand the tolerability, safety, efficacy, and unmet needs of DTG/3TC not only as defined by biomedical science, but also through an understanding of patients' perceptions and experiences. Critical Medical Anthropology 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. This will help us to not only provide evidence of patients' biomedical experiences of DTG/3TC, but also the ways they feel and speak about it, and the stories patients' share with each other about it. Having first-hand patient knowledge of DTG/3TC means ViiV Healthcare can improve their communication of the drug and that health care providers and support networks (e.g. Sussex Beacon, Terrence Higgins Trust) can improve communication with patients about their treatment and the future of HIV treatment.

4 RESEARCH QUESTION/AIM(S)

We have identified two primary research questions: *What are patients' experiences and perceptions of the safety, effectiveness, and tolerability of the 2-drug regimen DTG/3TC? What are the unmet needs of patients undergoing the 2-drug regimen?*

To explore patients' perceptions and experiences of the 2-drug treatment regimen DTG/3TC, including potentially unmet treatment needs.

4.1 Objectives

- To investigate patients' perceptions and experiences on the safety, effectiveness, tolerability, and unmet needs of the DTG/3TC 2-drug regimen
- To conduct comparative analysis of the safety, effectiveness, tolerability, and unmet needs between patients on the DTG/3TC 2-drug regimen and patients on other two-drug and three-drug combinations
- To provide recommendations that improve doctor-patient communication, knowledge and understanding of treatment plan, and additional care that ought to be considered in patient-centred, holistic care plans

4.2 Outcome

1. To identify patients' perceptions and experiences on the safety, effectiveness, tolerability, and unmet needs of the DTG/3TC 2-drug regimen
2. To share findings through published articles, at international conferences, and through public engagement
3. To inform the future direction of HIV treatment by providing evidence of patients' perceptions and experiences of 2-drug regimens
4. To improve doctor and patient communication by identifying patient fears, worries, misconceptions, and general concerns of their drug regimen and by providing specific recommendations to improve communication during public engagement

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYSIS

We will employ a qualitative study design with in-built processes for data analysis so that the study follows an iterative process and can be refined after each method. To generate a robust data set we will utilise three methods: cultural domain analysis (CDA), focus group discussions (FGDs), and in-depth interviews.[11] Triangulation of methods will ensure we have a valid and reliable data set that provides nuanced understanding of patient perception and experience. We will conduct all or some of the methods digitally or in person, depending on COVID-19 guidance from the UK Government and the University of Sussex; therefore the protocol will include a description of both in-person and digital methods and ethics, security and study limitations.

Digital Research and Platform

Isolation measures to contain the spread of COVID-19 means that our methods need to be adapted for the possibility that in-person interactions must be avoided. It is also possible that as lockdown measures ease in the UK and in-person meetings become allowed that participants prefer to take part in the study remotely and online. Social research has been conducted online for many years and we referred to Lupton (2020) or a comprehensive set of resources on how to 'do' fieldwork in a pandemic.

Although interviews and focus group discussions have long been adapted to be conducted online and via telephone, to our knowledge, cultural domain analysis has never been conducted from a distance or online. To inform how to adapt this method to online we consulted with the Brighton and Sussex Medical School (BSMS) Research Ethics Committee and BSMS Technology Enhanced Learning for guidance on ethics, platform, and method. We conducted a User Acceptance Study of the research methods to ensure they were adaptable and could still produce valid and reliable data. Results of the Study indicate cultural domain analysis can be adapted for online implementation and we are currently writing-up findings and recommendations for publication.

We followed the University of Sussex guidance published by the Research Ethics and Integrity Committee (REIC) on the use of video conferencing platforms in research (April 2020). In the guidance the REIC suggests researchers use Microsoft Teams, Microsoft Skype for Business, or Zoom for Education for video conferencing. The research for this project is considered 'highly confidential' thus we will seek to employ Microsoft Teams or Microsoft Skype for Business. However, when it is not possible or the research participants requests, we will use Zoom for Education.

We will also offer participants the option for us to call them by telephone for participation in CDA and IDIs. We feel this is a viable option to offer based on guidance from David Fray, protocol contributor, and his experiences with the HIV community at the Sussex Beacon. For CDA we will offer to telephone participants while we simultaneously log into the shared Padlet page to maintain the visual component of the method.

To maintain digital security, we will follow the REIC guidance and when possible avoid using the functionality built into Teams and Skype for Business to record interviews. Instead we will use a separate device, like an audio-recorder, that has a secure password. When it is not possible to audio-record or the participant prefers to use built-in recording functionality we will identify the default location where recordings are stored so they can be retrieved and stored securely. In Microsoft Teams recordings are stored in Microsoft Stream cloud upon which we will retrieve the recording and delete it from the cloud. Zoom for Education and Skype for Business allow for recordings to be saved locally on the computer. Files saved to the computer will be removed and deleted from our devices or file location and stored securely in University approved research storage, namely OneDrive. Files will be password protected within a specific folder. Recordings will be deleted once transcription and note-taking are complete.

Participants will be informed that interviews and focus group discussions will be recorded in the participant information sheet shared before the interview. They will be given the option for the researcher to record using built-in recording functionality or audio-recorded using a separate device. CDA, FDGs and in-depth interviews will be audio-recorded, checked for quality, and transcribed verbatim. Participants will also have the option of

whether they could like their camera on or off during CDA, IDIs, and FGDs. They will be informed of this option in the PIS and the RA will confirm their preference in email communication (see 11.12 Appendix 12- Participant Email Communication: draft script).

The research team has consulted with both BSMS ethics and Technology Enhanced Learning (TEL) for advice on security, ethics, ease of use, and accessibility. As a result, specific components of the study like text size and colour have been considered for improved accessibility and data outputs.

Study Design

This is a qualitative study design with emphasis on an iterative approach. Each phase of data collection and subsequent analysis is iterative, and key to developing insight and meaning into participant experiences and perceptions of the variables under study. [30] suggests that qualitative analysis is "a loop-like pattern of multiple rounds of revisiting the data as additional questions emerge, new connections are unearthed, and more complex formulations develop along with a deepening understanding of the material. Qualitative analysis is fundamentally an iterative set of processes". Our study design allows for an iterative process where CDA data is collected and analysed to identify patterns, themes, and categories. From these we will refine our interview and FGD questions to accommodate what has emerged from the data, rather than imposing frameworks onto participants.

This iterative process allows us to gain deeper insight into the variables under study and to, in turn, make more actionable recommendations. For example, cultural domain analysis will allow us to understand patients' knowledge frameworks regarding tolerability. We might begin to see a multiplicity in the meaning of tolerability, namely that it includes not just the management of drug side-effects, but also the management of treatment adherence/the commitment it takes to adhere to a specific regimen. Tolerability could thus have several levels of analysis - tolerability of the drug and tolerability of overall regimen. This has actionable implications for the funder, patient groups, and HIV treatment units because we now have conceptual understanding of what the variable tolerability means to patients in certain demographics and how it compares to the meaning prescribed by health care providers and pharmaceutical companies. Thus, when a health care provider asks patients how they are coping with the drug the patient may respond that they have minimal side effects. However, our study can provide suggestions for health care providers to probe deeper and perhaps ask how patients are coping with adhering to the treatment regimen. We anticipate we will uncover many linguistic and conceptual misalignments that will be actionable for the study stakeholders. Such insights could allow for better alignment in communication and treatment plans, and thus better health outcomes for patients.

Methods

Cultural Domain Analysis

First, Villa, Ackley, and the Research Assistant will conduct cultural domain analysis with 80-120 people (see section 7.2.1 for more on how sample size was determined). Cultural domain analysis is 'the study of how people in a group think about lists of things that somehow go together. The goal is to understand how people in different cultures (or subcultures) interpret the content of domains differently'.[12] In this study, cultural domain analysis will explore how people living with HIV and on dual or triple therapy treatments think about and interpret of the safety, effectiveness, tolerability, and unmet needs of DTG/3TC as compared to their current or previous treatments.

Cultural domain analysis is a type of structured interviewing method that is very productive because it is known to be enjoyable to administer, and it is an easy way to collect and analyse data from a large number of people. CDA will enable us to understand how participants perceive the factors that influence their treatments. The researchers will analyse the data according to the study variables to gain insight into what needs they have in treatment that are currently unmet by analysing for factors that positively or negatively impact unmet needs, as well as safety, effectiveness, and tolerability of treatment more generally, and DTG/3TC specifically. The primary variable we intend to explore with CDA is patient unmet need. Asking respondents to discuss the positive and

negative factors related to their treatment will allow us to analyse findings according to unmet need (see 11.4 Appendix 4 – Sample Cultural Domain Analysis questions and probes). We feel that analysing the data to understand this variable is a better approach than their directly asking patients to list unmet needs. 'Unmet need' is an analytical concept that many participants may not directly understand or may depend on the duration of their current treatment. Findings from a User Acceptance Study (UAS) conducted to inform how we adapt CDA from in-person to online support this. In the UAS we asked participants to list the unmet needs they have in either their kitchen, bathroom, or workspace. We found that unmet need was difficult to articulate, particularly in comparison to when we asked people to list the positive and negative factors in those spaces. We also found that unmet need was something that could only be realised over time. This led us to believe that patients newly diagnosed and just starting treatment, as well as patients who have recently switched drug-regimens might not know what their unmet needs are yet. They might only discover what needs are lacking after some time, thus indicating that analysing according to positive and negative factors will better illuminate any unmet needs. Findings from CDA will be further explored in IDIs and FGDs to ensure our analysis is consistent with patient experiences and perceptions expressed in other methods.

Within CDA the researchers will utilise the tools of free listing, pile-sorts, and ranking. When this method is conducted in-person we will ask participants to write their answers on notecards. When this method is conducted online, we will utilise Padlet, an application to create an online bulletin board that can be used to display information for any topic and if often used in digital learning.

Free listing is a simple method where participants are asked to list all they know about 'x,' and the goal is to get informants to list as many items as they can in a domain. We will first ask the target population to list the most important factors that positively/negatively impact their experience on DTG/3TC. We will ask the control population to list what they perceive to be the most positive/negative components of a DTG/3TC regimen (if they are unfamiliar with this particular combination then, with dual therapy more generally). Then, we will ask the target population to list the most important factors that positively/negatively impacted their experiences on triple therapy or alternative dual therapy combinations before switching to the DTG/3TC regimen. If the participant has only ever been on DTG/3TC, then we will ask them the most important factors that positively/negatively impact their current regimen. We will ask the control population to list the most important factors that positively/negatively impact their current dual or triple therapy regimens. Probing and prompting is essential in free listing and will be used carefully as to not guide respondent answers (e.g. 'are there any more you can think of?'). The discussion will be audio-recorded using a hand-held audio recorder and the free list will be either photographed (if conducted in person) or saved as an image (if conducted online).

Upon completing the free listing, we will ask participants to pile sort, or to 'put the terms together which they feel belong together'.[12] This is a simple and compelling method for collecting data about 'what goes with what'.[11] We will ask participants to put positive/negative factors together according to what they feel belongs together. Participants will be asked to describe the rationale for each of the piles created. The discussion will be audio-recorded using a hand-held audio recorder and the pile sort will be either photographed (if conducted in person) or saved as an image (if conducted online).

The final part of our cultural domain analysis is to ask participants to rank order their lists. We will have participants rank in order the positive/negative factors that most/least meet their treatment needs and support their quality of life while undergoing treatment. Participants will be asked to describe their rationale for their rank ordering. The discussion will be audio-recorded using a hand-held audio recorder and the rank list will be either photographed (if conducted in person) or saved as an image (if conducted online).

We will use the online tool Padlet to conduct the cultural domain analysis. At the start of the interview each participant will be sent a unique and confidential link to a new Padlet page via the chat function in Teams, Skype, or Zoom. The page will be linked to the researcher's personal data 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 researcher to observe the participant list, sort, and rank their domains in real time. The researcher

will export each Padlet board to an image and saved as data for the research team. At the end of the interview the research team will archive the Padlet session so that the board is taken off-line, and data is more secure.

Focus Group Discussions

Upon completion of cultural domain analysis Villa, Ackley, Clarke, and the Research Assistant will conduct preliminary analysis as part of an iterative approach to data collection and analysis. We will use initial insights gained from this first method to better inform the questions and probes Villa, Ackley, and the Research Assistant will ask in 3-6 FGDs with a total of 18-60 people, with 9-10 people per in-person FGD (or fewer depending on UK Government Guidance) and 6 people per online FGD (see section 7.2.1 for more on how sample size was determined). The difference in FGD group size for in-person versus online is because online FGDs tend to be more 'clunky' and 'prone to technology issues, lagging, internet dropouts, and interruptions' [29]. For these reasons the literature suggests that it is optimal to cap online FGDs at 6 participants [31–33]. Whether the FGD is in-person or online each FGD will have a moderator and a facilitator. The moderator will be responsible for the practicalities of the interview including; audio-recording and note-taking, supporting participants if there is a technical issue or if they need to leave the room, keeping track of the digital platform chat box, and letting participants into digital platform. The facilitator is responsible for guiding the discussion, asking questions, ensuring participants respect each other, and encouraging all participants to contribute.

Due to potential patient hesitancy to disclose their status to others in an FGD we are planning for a sample size that is variable in number (18-60 participants). When FGDs are conducted 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. When FGDs are conducted in-person we will use The Sussex Beacon meeting room to facilitate a more comfortable environment.

Focus group discussions will elicit patient perceptions and experiences of DTG/3TC and their current treatment regimen (see 11.5 Appendix 5 – Sample Focus Group Discussion questions and probes). We will aim to conduct 2 FGDs with each sample population, thus 2 FGDs with patients currently on DTG/3TC, 2 FGDs with patients on an alternative dual therapy regimen, and 2 FGDs with patients on a triple therapy regimen. In the FGDs with patients on DTG/3TC we will elicit patient experiences on the treatment and their perceptions before switching to it. In the FGDs with patients on other dual and triple therapy treatments we will elicit their perceptions of DTG/3TC and the future of HIV care and treatment more generally.

In-depth Interviews

Upon completion of the FGDs Villa, Ackley, Clarke, and the Research Assistant will, again, conduct a preliminary data analysis to refine our in-depth interview questions and probes. Villa, Ackley, and the Research Assistant will conduct 6-12 in-depth interviews with participants on DTG/3TC to elicit patient narratives and treatment histories of the regimen (see section 7.2.1 for more on how sample size was determined). In-depth interviews with the target population will allow participants to share specific experiences, fears, hopes, concerns, unexpected outcomes, etc. of the DTG/3TC therapy. We will analyse the interview data according to the variables of safety, tolerability, effectiveness, and unmet needs to provide case studies of patient experience. We will also conduct 6-12 in-depth interviews with participants on alternative dual therapy treatments, and 6-12 interviews with participants on triple therapy regimens. Interviews with the control population will allow us to learn about potential misconceptions, misunderstandings, rumours, gossip, knowledge gaps, etc. about DTG/3TC from patients on alternative therapies (see 11.6 Appendix 6 – Sample In-depth Interview questions and probes). This insight will help inform our recommendations to health care providers and ViiV Healthcare about unmet patient needs and the hopes/fears they may have about the future of HIV treatment; health education for patients before they change regimens to DTG/3TC; improved patient care, including potential psycho-social support for patients before and during their transition to DTG/3TC.

Limitations and benefits of digital methods

Social research has been conducted online for many years and there are many resources to support and examples of using online tools. We acknowledge that adapting methods that were initially planned for face-to-face use to a more 'hands-off' mode presents potential limitations and benefits.

The biggest limitation of adapting CDA to 'hands-off' mode is that there are no published resources or examples of doing this method online. After consultation with BSMS Research Ethics Committee and BSMS Technology Enhanced Learning we conducted a methodological User Acceptance Study (UAS) to 'test' the feasibility of this method online. In the pilot UAS had 21 participants who participated in CDA and provided feedback about their experiences and suggestions for improvement. The pilot included experienced social scientists, clinicians, patient representatives, and individuals not familiar with academic research and potentially lacking digital confidence. We also invited people with visual impairments, of different generations, and various caring responsibilities to imitate potential challenges in conducting the study online.

Online interviews are different from in-person interviews due to 'the role of the technology in facilitating real-time co-presence and interactivity' and 'the approach the interviewer takes to build rapport and curate the conversation' [29]. A vast amount of scholarship on how to conduct online interviews [34–36] informed our approach to the method; including how to structure an online interview and how to build rapport from a distance. Potential limitations include difficulties in assessing body language and building rapport.

FGDs are unique because of their focus on interpersonal interaction, however the dynamics change when conducting them online. In some cases, online groups can be 'particularly well-suited' to deal with sensitive topics [37].

Potential benefits of online research include increased anonymity due to the option to turn one's camera off or use a pseudonym. Additionally, accessing the online venue might be less of a barrier to participation than finding time to travel to the research location (ibid.).

Data Analysis

Each phase of data collection and subsequent analysis is iterative, and key to developing insight and meaning into participant experiences and perceptions of the variables under study. Berkowitz suggests that qualitative analysis is "a loop-like pattern of multiple rounds of revisiting the data as additional questions emerge, new connections are unearthed, and more complex formulations develop along with a deepening understanding of the material. Qualitative analysis is fundamentally an iterative set of processes".[30] Our study design allows for an iterative process where CDA data is collected and analysed to identify patterns, themes, and categories. From these we will refine our interview and FGD questions to accommodate what has emerged from the data, rather than imposing frameworks onto participants.

This iterative process allows us to gain deeper insight into the variables under study and to, in turn, make more actionable recommendations. For example, cultural domain analysis will allow us to understand patients' knowledge frameworks regarding tolerability. We might begin to see a multiplicity in the meaning of tolerability, namely that it includes not just the management of drug side-effects, but also the management of treatment adherence/the commitment it takes to adhere to a specific regimen. Tolerability could thus have several levels of analysis- tolerability of the drug and tolerability of overall regimen. This has actionable implications because we now have conceptual understanding of what the variable 'tolerability' means to patients in certain demographics and how it compares to the meaning prescribed by health care providers and pharmaceutical companies. Thus, when a health care provider asks patients how they are coping with the drug the patient may respond that they have minimal side effects. However, our study can provide suggestions for health care providers to probe deeper and perhaps ask how patients are coping with adhering to the treatment regimen. We anticipate we will uncover many linguistic and conceptual misalignments that will be actionable for the funder, clinicians, and community organisations. Such insights could allow for better alignment in communication and treatment plans, and thus better health outcomes for patients.

Quantitative data from the free listing, pile sorts and ranking will be analysed by Villa, Ackley, and the Research Assistant through ANTHROPAC; a program for collecting and analysing data on cultural domains. The program's analytical tools include techniques that are unique to Anthropology, such as consensus analysis, as well as standard multivariate tools such as multiple regression, factor analysis, cluster analysis, multidimensional scaling and correspondence analysis. In addition, the program provides a wide variety of data manipulation and transformation tools. We will conduct proximity analyse to compute measures of similarity and difference between respondents on DTG/3TC vs dual therapy vs triple therapy. We will also conduct consensus analysis to evaluate the extent and type of intracultural variability in the sample based on regimen and demographic variables. Villa, Ackley, Clarke, and the Research Assistant will summarise our findings from the cultural domain analysis by using standard descriptive statistics. Audio-recordings from FGDs and interviews will be checked for quality and transcribed verbatim in English (the language of data collection). Villa, Ackley, and the Research Assistant will code qualitative data in NVivo (version 12) according to standard qualitative analytical practices.[12] Data will then be analysed using applied thematic analysis to identify and describe both implicit and explicit ideas within the data. Applied thematic analysis is a more specific form of thematic analysis, which can be described as' a method for identifying, analysing and reporting patterns (themes) within data'.[38] Thematic analysis minimally organizes and describes a data set in rich detail through the active role the researcher plays in identifying patterns/themes, selecting which are of interest, and reporting describing them in text.[38] Applied thematic analysis (ATA) 'is a type of inductive analysis of qualitative data that can involve multiple analytic techniques'.[39] In ATA the researcher identifies key themes in the data that are transformed into codes (e.g. efficacy, tolerability, safety). Themes can be identified through word searches and data reduction techniques. Ultimately, ATA can be used to build theoretical models or to find solutions to real world problems. Such analysis may include comparing code frequencies, identifying code co-occurrence, and graphically displaying relationships between codes within the data set.[13]

Data Validation

We will employ several strategies suggested by[40] to validate our data. We will incorporate several methodological strategies to ensure the trustworthiness of our findings. We will account for any personal biases which may influence findings through reflexivity in our methods and approach. We will mitigate sampling bias through critical reflection of our recruitment methods at each stage of the research. We will keep meticulous records of our methods, sampling, data, and analysis to demonstrate a clear decision train and ensure interpretations of data are consistent and transparent. We have built in a control group to establish comparison cases to seek out similarities and differences across participant accounts. We will include rich verbatim descriptions of patients accounts as data to support findings. We will demonstrate clarity in terms of thought processes during data analysis and interpretations. In an effort to reduce bias we have built a research team of 4 people to ensure that variables, methods, and analysis are considered and discussed from several different perspectives. We can incorporate improved methods of validation by inviting participants to comment on their interview transcripts and whether the final themes and concepts created adequately reflect the variables under investigation. Finally, we have included data triangulation by including different methods to help produce a more comprehensive set of findings.

Research Integrity

The integrity of qualitative research can be defined by its trustworthiness, credibility, applicability, and consistency.[13] All efforts are in place in the design of this study to guaranteed trustworthy results: there is a robust and transparent description of the different methods that will be used, and a detailed account of how the data will be generated and analysed is provided. In order to ensure credibility of our findings, the researchers will adopt a neutral and non-judgemental approach in conducting the various phases of the study, not to influence patients' reported perceptions; furthermore, all results will be triangulated by the different methodologies (i.e. cultural domain analysis, FGDs, in-depth interviews), to further reinforce the validity and reliability of the findings. The rich sample size and the depth of some of the approaches are likely to generate a

robust data set. The HIV cohort in Brighton is largely composed by white men who have sex with men, and women and patients of non-white ethnicities represent a minority. All efforts will be put in place to ensure an adequate representation of these minority groups to ensure applicability of the findings in different contexts. We will target the Sunflower Clinic for an enriched recruitment of women: the Sunflower Clinic is a service available in Brighton dedicated to women living with HIV.

6 STUDY SETTING

The study setting will either be online or in person depending on the COVID-19 pandemic, guidance from the UK Government and the study sponsor, and research participant preference. The study will be conducted in person in Brighton, United Kingdom, at the Clinical Research Facility at the University Hospitals Sussex NHS Foundation Trust for the interviews and at The Sussex Beacon for the FGDs. Online the study will be conducted via Microsoft Teams, Zoom for Education or Skype for business. Data analysis and write-up will be carried out online with video conferencing when appropriate. Public engagement will be carried out in-person or online, depending on the COVID-19 pandemic and guidance from the UK Government and the study sponsor.

Participants accessed in-person will be at a pre-booked meeting room in the Clinical Research Facility at the University Hospitals Sussex NHS Foundation Trust or The Sussex Beacon at a time convenient for the participant. Participants accessed online will be able to join Team, Zoom, or Skype from a location of their choosing, although we will suggest participants have access to reliable internet, a laptop or tablet, and a private space. Participants accessed online can choose whether they would like their device's camera on or off and they can choose to use a pseudonym for anonymity (particularly during FGDs).

The research settings (online and in-person) will provide a confidential and comfortable space for participants to take part, both key elements in building rapport. Rapport is vital to the success of the project as participants need to feel safe and comfortable to share their experiences with the researchers. In-person we will provide refreshments and allow the participant to take breaks at any time. Online the participant can join from the comfort of their home, can opt to have the camera on or off, can use a pseudonym, and can take breaks at any time.

The same 'types' of activities will be carried out at each site with slight variation in implementation. For example, in CDA in-person participants will write answers on index cards and move them around. Online CDA participants will use Padlet to write answers and move them around the screen.

The only site-specific requirement to run the study online is that participants have access to the internet.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

The study population includes participants that are over 18, currently a patient of the HIV Department of BSUH, and on one of the therapies from our control or target population. We also aim to include participants that are from underrepresented populations including but not limited to women, minority ethnicity groups, trans-genders.

7.1.1 Inclusion criteria

Inclusion criteria includes that participants are

1. adults (aged 18 years old or older),
2. able to consent,
3. receive HIV care at the HIV Department of the Brighton and Sussex University Hospital (Lawson Unit/ Clinical Research Facility at the University Hospitals Sussex NHS Foundation Trust), and

4. on one of the following therapies
    a. control population
        i. Juluca (DTG/rilpivirine[RPV])
        ii. boosted darunavir plus lamivudine (DRV/r or DRV/c + 3TC)
        iii. boosted darunavir plus raltegravir (DRV/r or DRV/c + RAL)
        iv. a triple regimen (2 nucleos(t)ide reverse transcriptase inhibitors [NRTIs] + 1 InSTI; 2 NRTIs + 1 non-nucleoside reverse transcriptase inhibitor [NNRTI]; 2 NRTIs + boosted protease inhibitor [PI/b])
    b. target population
        i. DTG/3TC
5. All genders, sexual orientations, and socio-economic groups are eligible for participation

7.1.2 Exclusion criteria

Patients not fitting the inclusion criteria including those taking off-label drug combinations due to complex HIV resistance patterns; ART naïve or individuals declining ART will be excluded. Patients without access to the technology to participate in the online study will be given the option to participate in person (following COVID-19 guidance), and if this is not possible they will be excluded.

7.2 Sampling

This study includes a target and control group through purposive sampling. We suggest that the variables this study sets out to explore (i.e., safety, effectiveness, tolerability, and patient unmet needs) are best understood by including a control group. This is because DTG/3TC will not be experienced and perceived in isolation from patient's previous drug regimens or from other patients on different drug regimens. When a participant on DTG/3TC describes their experiences and perceptions they will be making a comparison to a 'time before' or to 'an other'. For example, we anticipate patients to describe current experiences of DTG/3TC effectiveness in comparison to a time they were on another drug regimen or in comparison to a friend/known person on another drug regimen (e.g. 'DTG/3TC is more effective than my previous treatment' or 'DTG/3TC seems to be less tolerable because my friend is on a different regimen and has fewer side effects').

This indicates we need to explore other drug regimens through a control group so that comparisons that arise in the data will have a reference point rooted in data. In short, if a patient says 'DTG/3TC is more safe than my previous treatment' we can understand not only experiences on DTG/3TC, but also how it compares to other treatments.

However, as the study design is iterative, we will first analyse the CDA data to identify if there is a justifiable distinction between initial findings within the control population, namely between the two and three drug regimens. If the CDA data reveals unique findings for the two and three drug regimens, then we will continue the study with a control group consisting of both two and three drug regimens. If the data does not reveals unique findings within the control group, then the control population for the FGDs and IDIs will be modified to include only patients on three-drug regimens while those on alternative two-drug regimens will be excluded.

Additionally, the subjective nature of these variables means that each person will have a different understanding, meaning, perception, and experience of the study variables. The funder, the sponsor, the researchers, and health care providers will have one, or more, way of defining the variables, but there is added value in exploring what they mean to patients. By widening our participant population to not just include the target population, but to also include the control groups we will gain a more in-depth understanding of what these variables mean to patients. This will ensure conceptual and operational alignment of the variables between patients and researchers. So, when we report findings from the study on safety or tolerability, there is conceptual and linguistic alignment.

The addition of the control group of patients on other dual therapies will allow us to tease out the peculiar characteristics of the dual DTG/3TC beyond the mere reduction of molecules employed for the treatment.

7.2.1 Size of sample

Out of a total HIV cohort composed by more than 2000 patients at BSUH, there are currently 40 patients on the 2-drug regimen DTG/3TC. We will approach all 40 patients on DTG/3TC to participate in the study; however, based on previous study recruitment at our centre we anticipate about 20% of those approached to consent. In the cultural domain analysis, we will recruit a minimum of 8 and up to 40 participants from the target population and 80-116 participants from the control population for a sample range of 80-120 participants. We aim to conduct 1-2 FGDs with each sample group (i.e. DTG/3TC, other dual therapy, triple therapy), with each FGD consisting of 6-10 people; thus our FGD sample size will be 18-60 people. We aim to conduct 6-12 in-depth interviews with patients on DTG/3TC, 6-12 interviews with patients on alternative dual therapies, and 6-12 interviews with patients on triple therapy giving an in-depth interview sample size of 18-36 people. We will approach the same participants for the CDA, FGDs, and in-depth interviews.

The sample size used in qualitative research methods is often smaller than in quantitative research. This is because qualitative research is most concerned with gaining an in-depth understanding of a phenomenon and is focused on meaning, which is centred on the how and why of a particular issue. In-depth interviews are 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 and emergent process. As such, the aim of the in-depth interview and FGD data is to create analytical, demographic, and ethnographic categories from the data and then to analyse relationships between categories while attending to how the lived experience of participants can be understood [41,42].

We acknowledge there is variability in what is suggested as a minimum sample size for qualitative research, and guidance in the literature can range anywhere from 5 to 50 participants [42]. Sample size depends on numerous factors including the quality of data, the scope of the study, the nature of the topic, the amount of useful information obtained from each participant, and the methods employed [43].

We intend to follow the principle of data saturation, or when the data collection process no longer offers any new or relevant data. In interviews Guest, et al. found that data saturation often occurs within the first twelve interviews while meta-themes might appear after six interviews.[44] We apply their findings to the IDI sample size and expect to reach data saturation in a variable sample size of 6-12 participants for each sub-group. In the data analysis process we will be transparent about our sample size sufficiency by noting when and by what metrics saturation was reached in each method [45]. If the researchers determine that saturation has not been achieved in any particular method, then the time period for participant recruitment will be extended to ensure that more data can be collected.

We acknowledge that participation in all three methods is a large commitment from the participants. We will encourage participants to take part in all three methods, but it is not required. We aim to recruit all DTG/3TC patients in the Lawson Unit, and will target underserved populations from the control groups. This should allow for a more representative sample amongst the entire participant sample.

Finally, we suggest that through the study design and methods we can achieve validity and reliability in qualitative research. The study design emphasises triangulation of methods (cultural domain analysis, in-depth interviews, FGDs), and each method collects different 'types' of data. Cultural domain analysis is a structured interview where the same questions will be asked of each participant, while in-depth interviews allow for flexibility in interview question probes, while FGDs allow participants to engage with each other and build on group discussion. Thus, one method is highly structured and requires a larger sample, one encourages flexibility and in-depth exploration of variables, and the other is based on dialectical processes in group settings. It is with a combination of methods and approaches that we feel confident we will achieve data saturation.

7.2.2 Sampling technique

We will use purposive sampling[11] to recruit a diverse population in terms of age, gender, socioeconomic group, ART, time on treatment, and number of previous ART regimes; particular attention will be placed on recruiting participants from underrepresented groups (i.e. older patients; women; people with history of challenges to adherence; people with co-morbidities). If we struggle to recruit participants through purposive sampling, then we will use snowball sampling[11] where existing study subjects recruit future subjects from among their networks (providing they meet inclusion criteria).

In purposive sampling, the researchers decide the purpose they want participants (or communities) to serve, and they recruit them. For this study the participants are on a specific drug regimen (DTG/3TC as well as alternative two and three drug regiments) and receiving treatment at a specific location (the Lawson Unit). In purposive sampling there is no overall sampling design that determines how many of each type of informant is needed for a study, rather the researchers recruit who is available and eligible. Purposive samples is used widely in (1) pilot studies, (2) intensive case studies, (3) critical case studies, and (4) studies of hard-to-find populations[11].

7.3 Recruitment

Participants will be recruited through several methods. The electronic clinical database will be screened and potential participants will be identified by members of the study team to be recruited during clinical sessions. Additionally, participants will be recruited through peer support groups; exercise, women's, and online groups at the Sussex Beacon; a study flyer for doctors to email or handed directly to their patients and to be circulated amongst the aforementioned groups, as well as amongst consultant group, nurses, and by the Research Assistant in or around the clinic (see 11.7 Appendix 7 – Participant Recruitment Flyer). Participants will be recruited through:

- Presentations to the Lawson Unit nurses and doctors (in-person or remotely);
- By sharing a digital version of the poster on the TV screen in the Lawson Unit;
- By sharing the flyer with Terrence Higgins Trust in Brighton;
- The Lawson Unit Brighton Sexual Health HIV research webpage;
- Promotion of the project via media channels such as radio stations, online/offline LGBTIQ+ magazines and newspapers, websites (e.g. More to Me Than HIV website), and TV channels;
- Attending the Lunch Positive Friday lunch club to share information and recruit participants (this is a lunch club offering subsidized meals for people living with HIV. It also offers a once a month dinner for PLWH who are over 50, and has just launched a befriending service for PLWH. They often invite guests, from charities and health sector, to be available to talk about their work to the meal attendees);
- The Sussex Beacon (it has a Service Users Forum, a Day Service (funded by Social Services), and a Women and Families Service, all of which can have invited guests, which can be a useful platform to promote interest in PEDAL);
- Peer Action (an organization run for, and by, PLWH; Peer Action organises health and social activities);
- The creation of a PEDAL website;

Clinical Research Nurses (CRN) will support participant identification and screening through the electronic clinical database search (2 hours a week for three months) and time dedicated to check patient eligibility. When approaching patients in the Lawson Unit waiting room, our patient representative David Fray will support us as a volunteer spending a day a week promoting and recruiting participants for PEDAL in the clinic.

Participation in the study will either be in-person or digital depending on the COVID-19 guidance. Participants will receive a patient information sheet (see 11.9 Appendix 9 – Participant Information Sheet) and will sign an informed consent form (see Appendix 11.10 Appendix 10 – Participant Informed Consent). Additionally, a participant recruitment poster (see 11.8 Appendix 8 – Participant Recruitment Poster) will be on the check-in desk in the HIV Department of the BSUH with information on the study and on how to become involved. If participation is digital, then participation will be offered by the consulting clinician at the end of a regularly

conducted phone consultation. If patients are interested in learning more about the study the clinician will obtain oral consent for the patient to be contacted by email with a digital participant information sheet and consent form.

It is our hope that clinical members of the research team will draw on existing patient-doctor relationships to make potential participants feel safe and comfortable in their deliberations of whether to consent. We have specific consent procedures in place that ensure there is no coercive element as patients may be in a dependent relationship with their doctors. These include obtaining consent at several stages of the study (for each method); through different means (oral, written, and informally through emails to set up digital meetings); and with different members of the RT (the research assistant, CA or GV) in addition to the initial recruitment approaches through doctors, nurses, etc. We also hope that positive patient-researcher interactions in the cultural domain analysis will help build rapport with potential FGD participants and make them feel comfortable to participate.

For both in-person participation a member of the research team will contact the participant by phone or email to schedule a day and time at the participant's convenience. Participants based in Brighton will be reimbursed for any travel costs incurred in travel to and from BSUH.

We also acknowledge that there are practical limitations to the study and we are hopeful that the study design will facilitate greater participant involvement for two reasons. First, we are offering participants a £10 voucher for their participation in each of the three methods (up to £30 if they take part in all of them), and we will also reimburse them for their transport to/from the hospital for study participation. Participants will be given a Love2Shop voucher card. Participants will also receive tea/coffee and will be able to suggest a time that works best for them. These accommodations may make potential participants more likely to participate. Additionally, the researchers have built rapport with patients in the Lawson Unit and the patient representative has built rapport with patients who are part of the Sussex Beacon network. This existing trust will help facilitate higher participation rates. Second, the methods selected allow participants to share experiences and feelings that they may not normally get the chance to express to health care professionals. The research provides a different platform for dialogue than participants might be used to and we hope this will appeal to them.

We will try to boost recruitment numbers for cultural domain analysis, and all methods, through the help of the HIV consultants and research nurses at the Lawson Unit and the Clinical Research Facility at the University Hospitals Sussex NHS Foundation Trust, patient representatives at the Sussex Beacon, information flyers posted and distributed at the Lawson Unit and the Clinical Research Facility at the University Hospitals Sussex NHS Foundation Trust, and on digital media. The research nurses will have access to patient information upon check-in and can screen for study eligibility without violating patient confidentiality. The research nurses will provide the patient with a study information sheet and a study researcher will approach the patient to obtain verbal consent that they would like to learn more and potentially participate (see 11.11 Appendix 11- Verbal Consent Checklist). If they consent the researcher will take the patient to a separate area and describe the study more in-depth and take informed consent before organising a day/time to conduct the methods. We hope that this approach will ensure we can reach data saturation.

7.3.1 Sample identification

Participants will be identified through purposive sampling by the research team with the help of several recruitment strategies. The first way we will identify participants is through a database screening in the Lawson Unit to determine eligible patients that clinicians and nurses can contract. Secondly, the patient's existing clinical care team will have access to patient records without explicit consent in order to identify potential participants, and to check whether they meet the inclusion criteria or before making the initial approach to patients. If the patient meets inclusion criteria the clinical care team will share recruitment materials and the participant information sheet.

Participants will be recruited publicly through several methods: (1) David Fray will share recruitment materials with his network at the Sussex Beacon and researchers will determine if participants are eligible to participate, (2) recruitment materials will be shared in the Lawson Unit reception and website, Brighton LGBTQ+ magazines, and the Brighton Terrence Higgins Trust and researchers will determine if participants are eligible to participate.

If a patient is identified by the clinical care team or through the public methods the referral process involves patients contacting the research team directly via the contact information provided on the recruitment materials and the participant information sheet. Additionally, the clinical care team can provide the contact information of the participant to the research team upon oral consent on behalf of the potential participant to be contacted.

If patients attend interviews or FGDs in-person they will be compensated in the form of vouchers as explained before.

7.3.2 Consent

The study involves several stages consent, including oral and fully informed consent. If participants are identified through a database screening by a member of the healthcare team, then they will seek oral consent via telephone, email, or in-person at the patient's next appointment to contact them with further information about the study. If participants are identified by the clinical care team during a clinic visit, then the clinical care team will obtain oral consent from the potential participants that we can contact them via telephone or email with further information about the study. If participants contact the research team directly, then we will first obtain oral consent to follow up regarding eligibility to participate.

Once participants have orally agreed to participate in an eligibility screening or for us to follow up with further information about the study we will begin the process of obtaining fully informed consent. We will communicate with participants in person, via email or telephone to inform them that we will provide them with a participant information sheet and an informed consent form for them to read, consider, and to ask us any questions about. We will then give participants the participant information sheet and an informed consent form either in person or send it over email. In the text of the email participants will be informed that they can ask any questions in email or we can phone them to answer any questions. Participants will be expected to return the signed and dated consent form before proceeding to the next phase.

Once the signed and dated consent form is received the research team will store it securely along with the participants preferences for the research to be in-person or online, for their preferred digital platform, whether they would like to have their video camera on or off, and whether they would like to use a pseudonym in any FGDs. These preferences will be obtained through oral or written communication with the research team prior to participation, but after consent has been obtained.

Prior to any CDA, FGDs, and IDIs the researcher conducting the interview or FGD will obtain oral consent to ensure the participant read and understood the participant information sheet and informed consent form. The participant will also have an opportunity to ask any remaining questions before participation in the method. The researcher will also conduct an assessment for capacity according to the guidelines that a capable person will:

- understand the purpose and nature of the research
- understand what the research involves, its benefits (or lack of benefits), risks and burdens
- understand the alternatives to taking part
- be able to retain the information long enough to make an effective decision.
- be able to make a free choice
- be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
- where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

Participants will be invited to join all components of the research; however, they may choose to take part in only the first method, the first and second method, or all three methods. Both written (either in-person or by email) and oral consent (in-person or on the digital platform, both audio-recorded) will be obtained before participation in each method.

If participants take part in more than one method, then both informed written consent and oral consent will be taken prior to each method. This means if a participant takes part in all three methods we will have a written and oral consent form for the CDA, a separate written and oral consent form for the FGD, and a separate written and oral consent form for the IDI.

8 ETHICAL AND REGULATORY CONSIDERATIONS

Ethical approval will be sought from the NHS REC ethical committee. All documents will be approved by the University's Sponsorship Sub-Committee (SSC). Patients will provide informed consent prior to enrolment either in person or through a document emailed to participants prior to each method. Participants will be asked to provide verbal consent before the start of each method. All members of the Research Team will complete training on Good Clinical Practice.

There are also the added ethical considerations of conduct research during a pandemic and the 'affective atmospheres' created 'when normal routines are disrupted and many people feel uncertain or worried, or are ill or caring for ill family members' (pg. 20).[29] However, people may be 'more confined, feeling bored or restless but in good health' and 'may welcome the opportunity to be part of a research project' (ibid.).

Participants will be able to stop the interview or FGD at any time and they will be free to leave. They will have the right to withdraw their consent or use of data collected at any time, upon which participant data will be destroyed (in the case of an FGD participant their responses will be deleted from audio recordings and transcripts). If participants exhibit distress or become upset during data collection the researcher will ask if they would like to pause or stop the interview or FGD. Participants will not have to answer any question they do not want. All data will be stored on password-protected computers and will be encrypted.

8.1 Assessment and management of risk

The research activities might illuminate several health-related issues; including the possibility that participants are not adhering to treatment regimens or that they are engaging in risky behaviour. It is also possible that the research might reveal that participants are suffering from poor physical, mental or social well-being and that is manifested through physical symptoms, low mood or social insecurities. In anticipation of these potential circumstances the research team will provide the name, contact information, and location of outreach services on the participant information sheet given to all participants at the time of consent. Additionally, the research team will encourage participants to speak with their clinician. Any potential risks to participants are communicated in the Participant Information Sheet.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study a favourable opinion will be sought from the Health Research Authority (HRA) (NHS Research Ethics Committee - REC). The Ethics Committee will have reviewed the present protocol, the patient information sheet, the consent form, and the advertisement used. All correspondence with the Research Ethics Committee will be retained and added as appendices to the study protocol.

Substantial and non-substantial amendments will be presented to the HRA. Only substantial amendments will be additionally considered by the NHS REC and will not be implemented until that review is in place and other mechanisms are in place to implement at site.

The Chief Investigator will produce an annual report (APR) for the REC and HRA and will notify them at the end of the study. The APR will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief

Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

Before enrolment of patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations will be in place. For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with the site (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

Amendments to the protocol will be submitted by the Chief Investigator to the University of Sussex Sponsorship Sub-Committee for review and approval. If deemed substantial by the Sponsor, the proposed amendment will be submitted to the Health Research Authority. Once approved, the protocol will be updated with the amendments in a newer version.

8.3 Peer review

The protocol will be reviewed internally by all members of the study team (G. Villa, C. Ackley, A. Clarke, D. Fray); by the Joint Clinical Research Office of the University of Sussex (D. Coton); by the Head of Department of Global Health and Infection of the Brighton and Sussex Medical School (M. Newport); by the lead research nurse of the Clinical Research Facility at the University Hospitals Sussex NHS Foundation Trust (L. Barbour), and by ViiV Healthcare (G. Hilton-Smith). External reviewers are A. Parkhurst (medical anthropologist at the University College London) and R Tan (social scientist at National University of Singapore).

8.4 Patient & Public Involvement

The study includes one/two patient representative(s) whose roles are described according to the INVO Patient and Public Involvement briefing.[46] Patient representatives have helped adapt in-person methods to online by taking part in a User Acceptance Study and providing feedback. They have reviewed and commented on the study protocol. They will help recruit participants from their professional networks. They will facilitate and support public engagement activities at the end of the study. Their role will be independent from the Sponsor and Investigators as they represent patients and the Sussex Beacon.

8.5 Protocol compliance

Accidental protocol deviations will be documented in dedicated forms, filed, and reported to the Chief Investigators and the Sponsor.

8.6 Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the Data Protection Act (2018) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Participant's identifying information will be replaced by an unrelated unique sequence of

characters (a combination of letters and numbers) 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 University Hospitals Sussex NHS Foundation Trust, whereas the anonymised data collected via the audio-recording of the FGDs and the IDIs (recordings and transcripts), and the images from the CDA, will be saved in a folder in the University of Brighton OneDrive. G. Villa, C. Ackley, A. Clarke and the Research Assistant will have access to the data. The Chief Investigator will be the data custodian. The data will be stored for the entire duration of the study until publication of the main findings and for a maximum duration of 12 months after its conclusion. All data will be subsequently destroyed.

8.7 Indemnity

The University of Sussex has indemnity insurance in place to cover its legal liabilities for this study.

8.8 Access to the final study dataset

G. Villa, C. Ackley, the Research Assistant, and A. Clarke will have access to the complete dataset, including the recordings of the FGDs and the IDIs, and the images and notes from the CDAs. Access to the appropriate sections of the dataset will be also granted to the MSc students engaging in some aspects of their research project for their MSc dissertation. All audio-recordings, images, and notes will be saved in a password-protected electronic folder, saved in the University of Brighton OneDrive.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

The main findings of the study will be written up and submitted to a HIV journal (e.g., *AIDS and Behavior*). A critical exploration of unmet patient needs and/or patient perceptions of the future direction of HIV research will be submitted to a journal at the intersection of anthropology and health (e.g., *Social Science and Medicine*). Both journals have the option to publish open access, which we have budgeted for appropriately. The main findings of the study be also made available at international conferences and on university repositories. Findings will be available to participants and the NHS Trust. Findings will be also shared in public engagement through the Sussex Beacon and Brighton and Sussex Medical School.

9.2 Authorship eligibility guidelines and any intended use of professional writers

Villa, Ackley, Clarke, Fray, and the Research Assistant will form the core of the research team and will be granted authorship in the publication of all the manuscripts arising from this research. First authorship and senior authorship of the manuscripts reporting the main findings will be shared between Villa and Ackley according to the nature of the publication (clinical vs social science/anthropology). Additional researchers will be granted authorship according to their role and input in keeping with the guidelines with the International Committee of Medical Journal Editors. Master students from the MSc of Global Health at the Department of Global Health and Infection will be invited to engage in the research and explore themes of their interest emerging from the CDA, FGDs and/or IDIs, such as stigma, for their Master dissertation. First authorship will be granted to the students if their results will lead to a separate publication.

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