Integrating U=U into HIV Counselling in South Africa (INTUIT-SA)

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Note: This version, updated July 30, 2025, contains a new section: 5.2.1.1 Protocol Changes Occurring During the Study. All new text is in italics.

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1. Main Title

The title of this project is, "Integrating U=U into HIV Counselling in South Africa (INTUIT-SA)"

2. Investigators and Institutions

The study will be carried out by a team of researchers from the Health Economics and Epidemiology Research Office (HE^{2}RO) of the Wits Health Consortium of the University of the Witwatersrand (WITS) and Boston University's Department of Global Health (DGH). Dr. Jacob Bor of the DGH at Boston University will serve as GDH Principal Investigator (PI). Dr. Dorina Onoya of HE^{2}RO will serve as the Wits PI. This protocol will be reviewed by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand and the Boston University Institutional Review Board (IRB). All South African individuals participating in this research will be the responsibility of the HREC of the University of the Witwatersrand.

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3. Summary

The near-elimination of HIV transmission with antiretroviral therapy (ART) has provided the world with a clear path to end the HIV epidemic through the mass provision of ART at diagnosis, i.e. test-and-treat. Despite the substantial prevention benefits of ART, we found minimal knowledge of treatment-as-prevention (TasP) in two population-based surveys we recently conducted in South Africa. Indeed, current public health messaging and clinical HIV counselling in South Africa do not emphasize the prevention benefits of ART. In 2016, U=U Campaign was launched to disseminate the scientific evidence that people with HIV cannot transmit the virus if their viral load is undetectable. U=U has been endorsed by NIH and by organizations in nearly 100 countries. Anecdotal evidence suggests providing information on U=U may reduce stigma and improve the wellbeing of PLWH, and may lead to increased ART uptake and adherence by appealing to the desire of PLWH to avoid transmission to others. Although the science on U=U is clear, there is currently a critical evidence gap on (a) how best to integrate information on U=U into HIV counselling services, and (b) what impact U=U messaging has on the wellbeing of PLWH and treatment-seeking behaviours.

We propose a formative research study (R34) to develop an app-based educational video intervention that will provide information on U=U that is locally-appropriate and can be integrated into routine HIV counselling. We will pilot the intervention in a clinical trial of patients receiving HIV post-test and adherence counselling services, to determine feasibility and acceptability, impact on U=U knowledge and attitudes, impact on stigma and psychological wellbeing, and preliminary evidence for ART uptake, adherence and retention, and viral suppression (primary outcome).

The study builds on a longstanding collaboration between Boston University and the Health Economics and Epidemiology
Research Office (HE2RO) at the University of Witwatersrand in Johannesburg, South Africa.
This study is highly innovative because we take a novel approach – disseminating information on the prevention benefits of ART – to improve the wellbeing of PLWH and motivate early uptake of ART in South Africa. The research will have significant public health impact as the findings have the potential to shape HIV counselling guidelines and practice in the country with the world's largest HIV epidemic. We hypothesize that selling treatment-as-prevention on its merits could substantially improve the wellbeing of PLWH and increase demand for ART, enabling countries to maximize the impact of test-and-treat.

4. The Study – Background, Rationale, and Objectives

4.1. Background

4.1.1. There is now scientific consensus: virally-suppressive ART virtually eliminates HIV transmission.

In the HPTN-052 trial, patients randomized to immediate ART were 96% less likely to transmit HIV to HIV-negative partners than patients randomized to deferred ART.[1,3] In the PARTNER-1, -2, and Opposites Attract studies, sero-discordant couples using ART for prevention had zero linked infections in over 126,000 condomless sex acts.[4] NIH and CDC leadership have strongly endorsed the science behind U=U.[24] Treatment-as-prevention (TasP) is the a primary public health rationale for test and treat.[25–27] Models predict test-and-treat will reduce incidence and could end the epidemic, but only with high uptake and adherence.[8–10,28] South Africa started test-and-treat in 2016.[27] Although there have been gains in treatment coverage, a 2017 population survey found just 52% of South African PLWH were virally suppressed.[13]

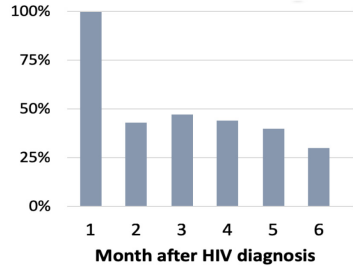


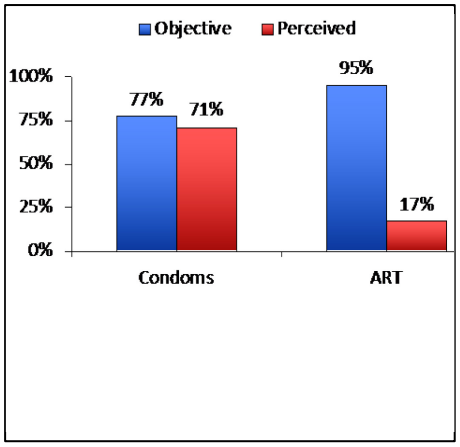
Fig 1. Percent retained in care after diagnosis in the UTT era. Figure shows share of patients (n=93) diagnosed with HIV who returned for clinic visits (including ART pickups) in each month.

4.1.2. Despite universal eligibility, there are gaps in demand for ART early in HIV infection.

UNAIDS set targets of 90% diagnosed, 90% started on ART, and 90% virally suppressed to guide progress towards universal test-and-treat.[28] Yet, our work - and that of others - has shown many PLWH present late for care,[29–31] many eligible people do not start ART,[32–36] and many who initiate do not stay on therapy.[37] The 2017 HSRC household survey found 85% of PLWH knew their status; of which 71% were on ART; and of which 88% were virally suppressed, implying just 52% of PLWH are virally suppressed. In a recent study of patient records at two clinics in Johannesburg led by Dr. Onoya, we found that under 50% of patients diagnosed in the test-and-treat era returned for their monthly drug pick-ups (Fig 1). In a systematic review of reasons for ART refusal led by Dr. Bor,[38] we found that many PLWH who did not start ART reported they did not yet feel sick and perceived little benefit from ART. Indeed, although START[39] and TEMPRANO[40] showed that early ART has clinical benefits, magnitudes were relatively modest. For a patient with CD4>500, it would take 60 person-years (PY) of ART to avert one serious but non-fatal adverse health outcome.[40,41] In our review of ART refusal, other PLWH cited risks associated with social isolation, stigma, side effects, and costs of care-seeking.[42–46] PLWH face real costs to life-long daily therapy. Yet many are unaware that virally-suppressive ART eliminates sexual transmission.

4.1.3. Knowledge of the prevention benefits of ART is limited.

In a recent survey of young adults in rural South Africa (Bor K01), we found major gaps in knowledge about HIV treatment-as-prevention (TasP). Using innovative methods to elicit quantitative beliefs,[47,48] we asked respondents about the chances of HIV transmission if a serodiscordant couple had weekly sex for a year without a condom, with a condom, and without a condom but with virally suppressive ART. Respondents overestimated risk of transmission on ART (Fig, Aims), reporting annual transmission probabilities of 75% on average. The objective transmission risk is about 1%. Participants vastly underestimated the efficacy of TasP (Fig 2), even as they had accurate beliefs about condoms. We found nearly identical results in a sample of 363 Gauteng university students: respondents perceived ART to reduce infection risk by 17%; in fact, the efficacy of TasP is >95%. Qualitative studies in South Africa have also found low familiarity with TasP.[49]



4.1.4. The U=U Campaign was developed to disseminate the science on TasP and reduce HIV stigma.

The "U=U" (Undetectable=Untransmittable) campaign was launched in 2016 by the Prevention Access Campaign (PAC), led by Bruce Richman, a consultant on this proposal . PAC's U=U Consensus Statement has now been endorsed by all the PIs on the major TasP studies, by over 800 organizations, and by NIH. PAC has conducted extensive advocacy and education on U=U (Fig 3), and developed social marketing materials. U=U campaigns are being implemented by organizations in nearly 100 countries. Still, U=U campaigns have not (yet) been widely implemented in sub-Saharan Africa. Evidence is limited on how best to message U=U and the impact of U=U information on stigma and ART uptake in sub-Saharan Africa.

Fig 3. U=U at AIDS2018

4.1.5. HIV counseling in South Africa does not emphasize U=U, even though it is a highly effective secondary prevention strategy.

HIV post-diagnosis and adherence counseling in South Africa does not emphasize the prevention benefits of ART.[50] (Couples' counseling is an exception but is relatively rare.) HIV patients starting ART are counseled to avoid transmission to others, but abstinence and condom use are recommended for secondary prevention.[51] The implicit message is that ART is not effective in preventing transmission, in spite of evidence that U=U. A recent study found that TasP is the single most effective secondary prevention strategy, more effective than condoms and pre-exposure prophylaxis (Fig 4).[15] TasP may even be preferred by PLWH: a qualitative study of sero-discordant couples in Kenya found a preference for TasP over PrEP for secondary

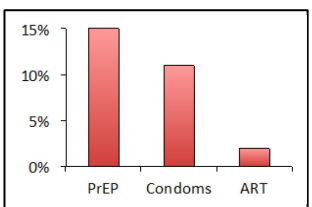


Fig 4. 10-yr transmission under three secondary prevention strategies

HIV prevention.[52] Though scientists and policy-makers have grappled with concerns of disinhibition, evidence from HPTN-052 and PARTNERS suggests lower infectiousness swamps any change in sexual behavior. Counseling on risks of STIs and pregnancy must be part of any TasP strategy. Nevertheless, TasP is highly effective and there is an ethical imperative to provide TasP information given gaps in condom use. In a recent study, 1 in 4 South African HIV patients not yet on ART reported condomless sex with an HIV-uninfected partner.[53]

4.1.6. U=U information can have positive impacts on psychological wellbeing of PLWH and reduce stigma.

A primary rationale to disseminate U=U information is the potential to destigmatize HIV, improve the mental health of PLWH, and improve positive associations and attitudes towards taking ART. Although systematic investigations are limited at this time, anecdotal evidence and testimonials suggests psychosocial benefits (personal communication, Bruce Richman, Sandra Dlamini). In a recent editorial, HIV clinicians Calabrese and Mayer write: "Education about U=U offers psychosocial benefits for individuals who are stably suppressed, alleviating self-stigma, relieving guilt surrounding potential transmission, and enabling sex without fear."[14]

4.1.7. U=U information provides a critical tool for PLWH who seek to reduce risk of transmission.

There is strong evidence that many PLWH are motivated to avoid transmitting HIV to others. A large literature on HIV prevention altruism reviewed by O'Leary & Wolitski[18] suggests many PLWH adopt significant changes in behavior to reduce the risk of infecting others, e.g. having less unprotected sex.[16–21] (A purely self-interested PLWH would have more unprotected sex upon learning their status, as risk of being newly infected is zero.[54]) In a key study supporting the scientific premise of this proposal, Dr. Rachel King (consultant) conducted a mixed methods study of PLWH in Uganda and found that HIV prevention altruism played a very strong role motivating PLWH to adopt protective behaviors and avoid transmitting the virus.[17] Dr. King's study is consistent with a large literature on HIV prevention altruism among MSM in the United States.[16,18,55,56] Although attempts to increase altruistic motivations have had limited success,[57] the literature suggests many PLWH are already altruistically motivated.[16–21] TasP offers a powerful tool to act on these motivations.

4.1.8. Integrating U=U into HIV counseling in South Africa could increase demand for ART.

HIV prevention altruism could be a powerful motivator for ART uptake and retention in the TasP era. Altruism was cited as a key factor in high adherence to ART in the HPTN-052 trial, in which HIV-infected study subjects were informed and counseled on the benefits of treatment-as-prevention.[58] Pregnant women also have high rates of ART uptake and adherence to prevent mother-to-child transmission, a related – though distinct – example of treatment-as-prevention.[59] U=U information may also increase the perceived psychosocial benefits of ART uptake and

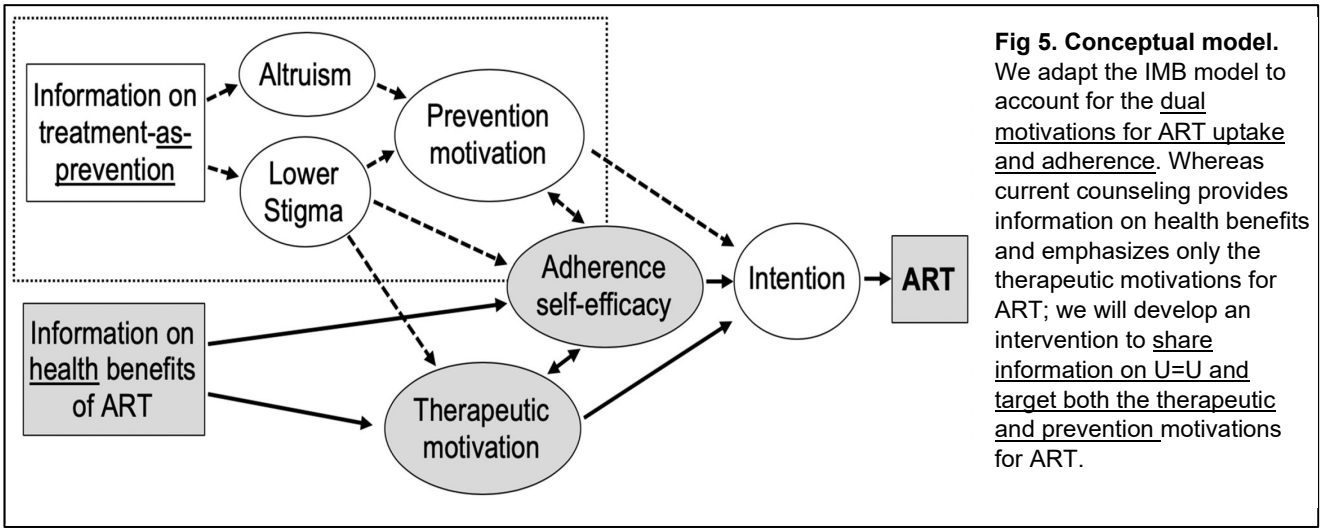


Fig 5. Conceptual model. We adapt the IMB model to account for the dual motivations for ART uptake and adherence. Whereas current counseling provides information on health benefits and emphasizes only the therapeutic motivations for ART; we will develop an intervention to share information on U=U and target both the therapeutic and prevention motivations for ART.

adherence, with potential to reduce transmission anxiety and lower internalized stigma.

Fig 5 displays our conceptual model. We adapt the Information-Motivation-Behavioral Skills model[60] to account for dual motivations (therapeutic vs. prevention) for ART uptake and adherence. The model illustrates how a major rationale and motivation for starting and staying on therapy is currently omitted from HIV counseling. Although

knowledge alone is not enough, in the absence of accurate information on U=U, existing motivations to avoid transmission and behavioral skills to start and stay on ART may not be activated. For some PLWH, information on U=U may be the missing link.

In addition to providing information on U=U, our intervention will target factors that activate prevention motivation, drawing on theory from the literature on HIV Prevention Altruism as well as anecdotal reports from the U=U campaign. Research suggests that people are more likely to behave altruistically when they derive psychic benefit,[61] which is thought to occur when the action is consistent with a person's core values. O'Leary & Wolitski link HIV prevention altruism to Bandura's concept of moral agency.[18,62] We will therefore highlight different values that may underpin prevention motivation, e.g. commitments to family, partners, citizenship, and faith.[63] Nimmons & Folkman[56] and King[17] describe the varied narratives that support HIV prevention altruism: e.g. PLWH were not only motivated to protect their partners but also to feel like they were part of the solution to the epidemic. **U=U** information may also enhance therapeutic motivation for ART by reducing internalized stigma, improving mental health, and supporting the development of a positive self-image associated with ART.[14] Finally, by presenting testimonials from South Africans using TasP, the intervention will normalize TasP and address perceived barriers to using TasP, thereby increasing self-efficacy to use TasP.[62,64]

4.2. Rationale

Our preliminary studies support the scientific premise of this R34: that integrating U=U information into HIV counseling could increase ART uptake and adherence and improve wellbeing of PLWH. We have shown:

- Many PLWH in South Africa do not start or stay on ART despite being eligible (Bor / Onoya analyses)[31,33]
- PLWH who do not start ART perceive the costs of early ART exceed the benefits (Bor systematic review)[38]
- Awareness of TasP is very low, as we found in two separate population-based surveys (Bor K01)[48]
- Many PLWH are motivated by "HIV prevention altruism" to limit transmission (King mixed-methods study)[17]
- Current HIV counseling does not provide this information (Onoya mixed-methods study)[65]
- The U=U Campaign was launched in 2016 to disseminate the science of TasP (Richman)
- An informational video on health benefits of ART increased perceived longevity among PLWH (Bor/Inglis)

In light of these preliminary data, this R34 will design and pilot an educational video-based "app" to deliver information on U=U and support HIV prevention altruism among PLWH presenting to public sector health clinics in Gauteng, South Africa. Our scientific contribution will be the development of a feasible, acceptable, and effective intervention that can be rapidly scaled. Our research will also generate a deeper understanding of the role of altruism in motivating behavior change. The research will have significant public health impact because it will inform the design of effective HIV counseling and public messaging around U=U, to maximize the benefit of HIV test-and-treat.

4.3. Aims and objectives

We will develop and pilot a video-based "app" focusing on U=U messages and altruistic intentions to support HIV counseling in South Africa. Educational videos offer an efficient, standardized approach to deliver accurate and multidimensional information and can be integrated with existing HIV counseling. The study builds on a longstanding collaboration between Boston University and the University of Witwatersrand, extensive preliminary data, and will be carried out in public clinics where we have worked.

Aim 1. Develop a video-based "app" to provide HIV patients with information on TasP/U=U.

We will design a series of short video modules on the prevention benefits of ART leading to viral suppression and package them as a tablet-based app to augment existing HIV counseling. In collaboration with the Prevention Access Campaign, we will develop locally-appropriate videos on (a) the science of TasP/U=U including risks, (b) benefits to self (e.g. psychological benefits, ability to have children), (c) benefits to partners (e.g. secondary prevention), (d)

benefits to society (e.g. AIDS-free generation), and (e) TasP self-efficacy, including viral load (VL) literacy, disclosure, and couples testing. Content will be developed with HIV counselors, PLWH, and other stakeholders in an Intervention Mapping exercise.23 After training clinic staff, the videos will be shown in clinic waiting rooms and the tablet-based "app" will be integrated into HIV counseling sessions. Intervention content will also be pushed to participants via SMS, and the app will be shared with those with smart phones. The intervention will be pre-tested in focus groups (n=3) and interviews (n=20) with counselors and patients. We also plan to hold 4 additional focus groups of 10 people each (n=40). The focus groups will include people living with HIV or HIV counselors. These additional focus groups will help inform the development of our intervention.

Aim 2. Establish intervention acceptability, effects on knowledge and attitudes, and preliminary impact on ART uptake, adherence, and viral suppression in a pilot trial and demonstration project (n=135).

We will pilot the intervention at three public sector clinics. During recruitment period 1 (n=90), patients completing HIV post-test or adherence counseling will be referred to study staff and randomized 1:1 to no intervention (Arm A) vs. "controlled exposure" to the tablet-based U=U app (Arm B). In recruitment period 2 (n=45), U=U videos will be shown in clinic waiting rooms and the tablet-based app will be integrated into routine counseling (Arm C) in a "clinical exposure" demonstration project. All participants will be cross-randomized to monthly text messages reinforcing intervention content. For all study arms, we will assess feasibility and acceptability, resonance of different key messages and videos, knowledge and attitudes related to TasP, internalized stigma and mental health, HIV prevention altruism, and behaviours related to disclosure, risk-taking, and care-seeking in surveys at enrolment, post-test, and 6 months. ART uptake, appointment adherence, and 6-month VL will be assessed in clinical records. Qualitative exit interviews will be conducted with participants and staff (n=30).

5. Study design and study participants

5.1. Aim 1. Develop a video intervention to provide HIV patients with information on TasP/U=U.

5.1.1 Rationale.

We will design a locally-appropriate U=U educational video intervention, which will provide information on the prevention benefits of immediate ART uptake and adherence leading to viral suppression. Currently, post-test HIV counseling does not emphasize U=U. In the general population – and even among some HIV counselors – knowledge of U=U is incomplete. Yet U=U campaigns have been reported to reduce internalize stigma and improve mental health and wellbeing of PLWH, leading to calls for "universal counseling on U=U" by leading HIV clinicians.[14] By providing accurate information on U=U, there is potential to improve wellbeing of PLWH and increase demand for early ART, leading increased adherence and viral suppression.

5.1.2 Intervention Mapping.

We will undertake an "Intervention Mapping" (IM) process[23] to design a feasible and locally acceptable intervention, building on existing social marketing materials from the U=U Campaign. The IM process will be chaired by Dr. Onoya, who has experience leading a similar process for her HIV counselor capacity-building study. The table below presents a summary of the steps in the IM process. Dr. Onoya will convene and facilitate an Intervention Development Working Group (IDWG) including key stakeholders and experts, described above. The IDWG will be made up of the research team, client representatives (persons living with HIV), provider representatives from the study sites including counselors and other health care providers, and experts described above. Additionally, a representative from the national association of people living with HIV (NAPWA) will be invited to participate in the process as well. The IDWG will meet eight times over the course of Year 1 to work through the six IM steps (Table) under the guidance of the PIs. In Y2-Y3 we will reconvene the IDWG to report back on study progress and results. Leveraging the expertise of the research team, patient community, and providers, the IDWG will guide the PIs in developing a locally-appropriate educational video intervention that clearly addresses both benefits and risks with U=U. The IM process will also build support for the intervention among clinic staff, PLWH, and other stakeholders.

Steps of Intervention Mapping Sessions planned for Intervention Development Working Group (+consultant)

Intervention development steps	**Stakeholder workshops/sessions**
Step 1. Logic model of the problem	Session 1. Introduce project and build consensus around the science of TasP
Step 2. Program outcomes and objectives	Session 2. Develop working model of U=U impact including HIV prevention altruism and internalized stigma, drawing on theory and the experiences and expertise of the IDWG. Review project outcomes and objectives. (Richman, King)
Step 3. Program design	Session 3. Identify key messages on TasP that would resonate with PLWH, and discuss narrative devices to support key messages (Richman, King, Inglis)
	Session 4. Discuss barriers to uptake and potential unintended consequences and risks associated with U=U, and craft clear messages to address these concerns.
Step 4. Program production	Session 5. Develop a storyboard for the educational videos providing information on TasP and targeting altruistic motivations (Inglis)
	Session 6. Obtain feedback on the videos and propose revisions (King)
Step 5. Program implementation plan	Session 7. Review and obtain feedback on the implementation plan. Obtain feedback on intervention materials including navigation within the tablet-based app (Steyn)
Step 6. Evaluation plan	Session 8. Obtain stakeholder feedback on evaluation plans. Report back to stake-holders
	Session 9. Report back on study progress (Year 2)
	Session 10. Report back on results and dissemination strategies (Year 3)

5.1.3 Development of U=U video content.

The educational video intervention will disseminate scientific information on U=U in a culturally-appropriate manner, designed to be acceptable for a patient population with varying levels of literacy and numeracy. Also, the intervention will also target key theoretical constructs of our conceptual model, as shown in Fig 6. As a starting point for the intervention, we will draw on existing video-based social marketing materials developed by the Prevention Access Campaign, which consultant Bruce Richman has offered to share (letter), and will adapt these for the South African context. Consideration will be given to particular narratives needed to support U=U messaging in this local context; challenges to using TasP that need to be addressed; and specific voices of authority – e.g. health workers, serodiscordant couples – that can most credibly deliver information on U=U. Dr. Richman will participate in Intervention Mapping sessions two and three, contributing to the logic model for U=U information impact, and sharing from the successes and challenges faced by prior U=U campaigns. Dr. King (letter) will also participate in IM sessions two and three to contribute theory on HIV prevention altruism and shape the intervention key messages.

The intervention will involve an introductory video on the science of U=U, highlighting scientific evidence from the HPTN-052 and PARTNER studies and the global consensus that U=U. We will then develop several video modules in collaboration with the IDWG. We anticipate modules highlighting:

- The Science of U=U, emphasizing viral suppression as the basis for efficacy, and discussion of benefits and risks
- The benefits to partners, including efficacy of TasP as a secondary prevention strategy for PLWH in different relationship contexts, and emphasizing different motivations underlying HIV Prevention Altruism
- The benefits to society, highlighting UTT guidelines and the potential for TasP to end the HIV epidemic
- The benefits to self, emphasizing psychological benefits related to positive self-image, less internalized stigma, and the ability to have relationships and a family without risk of transmitting HIV to partners or children

- The TasP modeling, emphasizing how PLWH can operationalize TasP in their lives, including viral monitoring, talking about U=U with others, disclosure to partners, couples testing, and building self-efficacy to use TasP
- The health benefits, although not directly related to U=U, we will additionally present information on the health benefits of ART using an excerpt from the "I'ksasa Elihle" (a Beautiful Future) Dr. Bor developed for his K01 in collaboration with Mr. Inglis, consultant on this project (letter), and Jive Media-Africa

Our intervention targets the dual motivations for ART—prevention and therapeutic—in Figs 5 and 6. Our work in Uganda[17] (King) and that of others indicates that many PLWH are strongly motivated to avoid transmission to partners and may also value the broader societal benefits. Thus, for some PLWH, the U=U intervention may enhance prevention motivations for ART uptake and adherence by appealing to existing HIV prevention altruism. A second channel for impact goes through therapeutic motivations for ART. Our review[68] found that many PLWH choose not to start ART because they do not think of themselves as "sick" and do not want to be reminded daily that they are HIV-infected. U=U information provides an alternate rationale for taking pills without these negative associations and may reduce internalized stigma. For some PLWH the U=U intervention may enhance therapeutic motivations for ART by destigmatizing HIV and offering a positive self-image associated with ART. Additionally, information on U=U could reduce the costs of disclosure to partners, and increase motivations to use ART as prevention. Finally, U=U information alone is likely insufficient to enable people to operationalize that information in their lives. HIV counseling already emphasizes generic adherence skills and self-efficacy. The intervention will build self-efficacy to use TasP by modeling via personal narratives how other people have integrated TasP in their lives. In particular, the intervention will emphasize behavioral skills related to viral monitoring, status disclosure, and couples testing, and counselors will be trained to reinforce these messages.

5.1.3.1 Filming the intervention content.

To develop new content for the U=U video modules (Fig 6), we will partner with Robert Inglis (consultant) and Jive Media Africa, a South African educational media company that specializes in public health video communications. Mr. Inglis, Director of Jive Media, is an expert in film-making and has developed HIV-related video interventions for multiple NIH-funded projects in Africa. We will develop the storyboards for each of the video modules in collaboration with the IDWG and Mr. Inglis will participate in IM Sessions three and five. Key informants including PLWH and health workers will be identified by the IDWG to share their stories, adding narrative to increase the salience and relevance of the videos. Jive Media will conduct all video filming, editing, and production.

5.1.3.2 Pre-testing video content in focus groups (n=24 patients across three focus groups).

After a first-round of filming and editing, "first cut" video modules will be shown and discussed in three focus groups (n=8 each) of PLWH accessing care at public sector clinics. Participants will be recruited from public sector clinics via referral from lay counselors after diagnosis and at drug pick-ups. We will recruit purposively to ensure representation of young adults (>75% 18-35 years), the age group least likely to be on ART and mostly likely to find U=U relevant. To foster open discussion, one focus group will be women only, one will be men only, and one will be mixed (>30% men). Feedback will be obtained on the clarity of the key messages in the videos, level of engagement, and the appropriateness and relevance of the information for their lives. FGDs will be recorded, transcribed, and translated. Led by Dr. Onoya (PI), we will use semi-directed content analysis to code the data based on theory as well as emergent themes.[69] After FDGs, intervention "final cuts" will be developed with Jive Media.

5.1.4 Integration of U=U videos into an interactive tablet-based app.

In order to facilitate integration of the educational videos into HIV counseling, the video modules will be delivered via a tablet-based App. The App will be developed in collaboration with Khanyisa Real Systems (KRS) a software applications development firm in South Africa with extensive expertise in app development (letter, KRS). The App will give participants active control to re-watch specific videos and will enable HIV counselors to refer participants to specific material that may be most relevant to their live discussions in the counseling session. Additionally, the App will enable us to integrate questions about video content into the modules and to ask participants to "rate" videos across different domains. Based on principles of active learning,[70] we expect that adding these participatory elements to the videos will increase cognitive engagement with the material and facilitate deeper learning. It will also enable self-tailoring, whereby participants whose responses to comprehension questions are incorrect can be encouraged to re-watch that module. Finally, through these questions, we will be able to collect data on which particular video modules were most – and least – successful in conveying key messages, and to evaluate the video

modules for participant engagement and acceptability. The app will be designed with low-resolution versions of the videos stored locally, so the app can be offered to be shared with study participants who have smart phones via Bluetooth without the participants incurring data fees. Participants, regardless of whether they have a smartphone, will be offered a branded information sheet covering the key messages of the video modules, and will receive regular SMS text messages on the key messages for the duration of the study.

5.1.5 Pre-testing the "App" to determine feasibility (n=20 patient interviews, 4 counsellors).

Following Orsmund & Cohn,[71,] we will assess feasibility regarding recruitment and retention, data collection, intervention procedures, and study management. We will track process measures (e.g. numbers recruited per week, whether participants successfully complete all study activities), review field notes of study staff in weekly team meetings, and conduct n=20 interviews with clinic staff and patients. We will assess the feasibility of three intervention modalities included in the trial (Aim 2): controlled exposure to the app in a study setting, clinical exposure with the videos shown in the waiting room and the app integrated into HIV counselling, and the supplementary text-message exposure designed to reinforce messages from the app. We will assess feasibility as follows:

Controlled exposure (n=10). We will pre-test the video intervention and survey instruments with ten people receiving HIV care, recruited from clinical settings. These pre-tests will provide data on whether changes are needed to the "app", videos, data collection, and study procedures before the pilot.

Clinical exposure (n=14). We will pre-test showing the videos in a waiting room and training counsellors to use the tablet-based app as a resource to support counselling. The clinical exposure in the waiting room will be done to determine whether the videos are visually appealing enough to draw the attention of patients in a busy waiting area. However counselling will not assume that they saw the videos and standard counselling will continues. We will conduct interviews with ten patients and several counsellors (take all, ~4 per site). Counsellors will be recruited into the study with permission from the facility manager. Lessons will be incorporated into a counsellor training manual for the pilot (Aim 2).

Text messages. We will develop and pre-test an automated system to send monthly SMS/text messages on U=U to study participants and to log responses. No actual participants will be included in the pre-test.

5.1.6 Pre-testing the survey instrument.

The feasibility assessment will also include a pre-test of survey instruments that we will use to assess key self-reported outcomes: acceptability of the intervention; beliefs, attitudes, and behaviors related to TasP; and constructs related to HIV prevention altruism and stigma. To assess the validity of survey scales for this context, we will use cognitive interviewing techniques,[72] asking participants how they arrived at their answer.

Acceptability of the intervention. Following the Technology Acceptance Model,[73] we will assess feasibility and acceptability of the U=U video-based "app" with respect to ease of use and usefulness domains. Each will be assessed with quantitative items to asses acceptability and open-ended response items to determine how to improve acceptability. Examples are in the box. We will also elicit Yelp-style 5-star rapid reviews for each of the intervention video modules independently to identify which videos resonated most and which may have elicited negative responses. Modules that score at least 4/5 5 stars will be retained for the intervention. Modules that score less than four stars will be revised, if limitations are clear, or dropped.

Beliefs about the prevention benefits of ART. We will include questions on beliefs about the probability of HIV transmission under different scenarios using an interactive approach to eliciting subjective probabilities that we have validated in South African young adult populations (Bor K01). We will also ask qualitative Likert-scale questions on attitudes towards different secondary prevention methods. We will assess beliefs about health benefits with similar methods.

Mechanisms. Theory predicts impact of U=U information will be greatest among people with altruistic preferences. To assess general altruism, we will pre-test the Rushton self-report altruism scale (20 items, Chronbach Alpha=0.89), which emphasizes altruistic actions.[74] We will also pre-test the altruism scale used by Dr. King (co-I) in her Uganda study (14-items), which focuses on altruistic attitudes rather than actions (e.g. "It is most important to look out for yourself, even if doing so comes at the expense of others").[17] We will assess HIV Prevention Altruism with the Nimmons-Acree-Folkman scale (7 items, Chronbach Alpha =0.91) used in studies of secondary HIV

prevention.[16,55,56,75] We will also construct and pre-test questions on HIV prevention altruism based on Dr. King's work in Uganda, e.g. "I worry about infecting my partners", "I want to protect the next generation from getting HIV", "It is only fair to try my best to avoid transmitting to others".[17] U=U information may also reduce internalized stigma and improve mental health. We will pre-test the internalized stigma questions used in the PopART trial: "I think less of myself…; I have felt ashamed…; I have lost respect or standing in the community because of my HIV status"[76]. We will also pretest the Hopkins Symptom Checklist-2577 to measure emotional distress and depression. Finally, we will pre-test modules on ART self-efficacy (HIV-ASES78) and locus of control (IPC scale[79]) which may mediate ability to translate intention into action.

5.1.7 Scientific rigor of the approach to Aim 1.

Aim 1 will develop an educational video-based intervention to provide information on U=U. The approach is scientifically rigorous because:

1) We are using Intervention Mapping[23], an established method to engage stakeholders in intervention development, to create an intervention that is feasible, locally-appropriate, and with a high likelihood of impact.

2) The intervention will incorporate rigorous scientific evidence on U=U into HIV counseling

3) The intervention is informed by behavioral theory, adapting the IMB model to account for the dual motivations – prevention and treatment – for ART, and the potential impact of U=U information on each.

4) We will used rigorous qualitative methods to improve the intervention using focus groups and individual interviews to assess the feasibility and acceptability of the intervention during the development phase

5.2. Aim 2. Establish the acceptability of the intervention, effects on TasP knowledge and attitudes, and preliminary impact on ART uptake and adherence in a pilot trial and demonstration project

5.2.1. Overview.

We will conduct a pilot clinical trial to assess the feasibility of implementing the intervention in a primary care clinical setting, determine its acceptability to patients and providers, evaluate its impact on knowledge and attitudes toward TasP, and assess preliminary impact on ART uptake and adherence. The pilot will consist of two phases: a patient-randomized trial of the tablet-based intervention vis-à-vis control in order to rigorously test intervention content (n=90), and a demonstration project assessing feasibility of integrating the intervention into HIV counselling at the facility level (n=45).

5.2.1.1 Protocol Changes Occurring During the Study (text added 7/30/2025)

Our original protocol specified that after conducting the RCT (Arm A vs. Arm B), we would conduct a non-randomized clinic-level demonstration project (Arm C) with the App videos shown in clinic waiting rooms. In a protocol deviation, the first 55 participants enrolled in Arms A and B received counseling on HIV TasP/U=U from one of our enumerators during the recruitment phase and coaching on the post-test knowledge questions, regardless of study arm. This data collection error means that both intervention and control participants (Arms A and B) would have received some exposure to HIV TasP/U=U content, attenuating any impact of the intervention. It also means that our analyses of the post-test knowledge and attitudes questions must omit these 55 participants. After recognizing this error, study staff were retrained and recruitment was separated into wave 1 (n=55) and wave 2 (n=80). Following the above protocol deviation, to improve power for our primary comparison, Arm C was dropped and the planned (n=45) participants were distributed to intervention (Arm B) and control (Arm A). Our main analyses include all 135 participants in Arms A and B; in sensitivity analyses we restrict the data to Wave 2 when there was no contamination of the control group.

Our original protocol specified a six-month follow-up survey that would assess changes in patient knowledge, attitudes, and mental health over time. Due to COVID-19 related delays, we were unable to conduct the six-month follow-up survey; hence, we report only on immediate post-test knowledge and attitudes and on clinical outcomes through 10 months, extracted from patient charts. All pre-specified outcomes relying on six-month follow-up surveys were not collected and are not reported on.

Our original protocol specified "VL<50 copies/ml at 6-10 months" as the primary outcome. During the study, a change in national guidelines shifted the timing of the first VL from 6 months to 3 months after ART initiation, leading us to expand our window of observation to 3-10 months. For our primary outcome, we raised the threshold for viral suppression from VL<50 to VL<200 copies/ml, because many patients do not reach VL<50 within 3 months even if they adhere to ART and to be consistent with WHO guidelines specifying <200 copies/ml as indicating zero transmission risk. We additionally report on <50 and <1000 VL thresholds.

Our original protocol specified several clinic visit adherence and retention measures that could not be estimated due to unforeseen limitations. Due to missing dates of next appointments in patient charts and variability in 1-month and 2-month prescribing, we were unable to compute "days late for next appointment" or "days without medication", concepts that underpinned two of our three pre-specified retention measures. In lieu of these measures, we defined new, simplified measures to capture longer-run retention concepts. These measures – any ART refills after 30 days; any ART refills during months 1-2, …months 3-4, and …months 5-6 – are robust to 1- and 2-month prescribing, and do not rely on accurate recording of future appointment dates.

These changes are indicated in the relevant places below in this protocol and are reflected in the current record at ClinicalTrials.gov (NCT04504357).

5.2.2. Study population and recruitment.

The study population will include adult men and women (18 years and older) receiving routine HIV counseling services at three public sector clinics in Gauteng, South Africa during the study period. Under current standard of care, HIV counseling is provided at two points in time: after an HIV diagnosis (post-test counseling) and after an elevated viral load (adherence counseling). The same counselors provide both services and the study will recruit from both populations, with at least 1/3 from each group. After their visit to the HIV counselor, patients will be referred to study staff for recruitment into the study. Study staff will explain the study, assure the patient that participation is voluntary, and obtain written consent if the patient wishes to enroll. Across the two study phases, we anticipate recruiting a total of n=135 adult men and women receiving HIV counseling services at three public sector clinics in Gauteng, South Africa. (This sample size is feasible – in a prior study we enrolled 600 newly diagnosed PLWH at four clinics in six months.)

Participants who enroll in the study will participate in surveys at enrolment and at 6-months follow-up. The baseline session, including consent (5 min), intake survey (10 min), intervention (if Arm B) (15min), and immediate post-test survey (25 min), is expected to take 45-60 minutes.

Inclusion / Exclusion: All individuals who receive HIV counseling services, are over 18 years, do not have acute care issues, and are able to consent will be offered enrolment in the study. Patients with acute medical needs who are referred for additional care will not be eligible, so as not to interrupt their care. Patients under 18 years are not eligible. Finally, patients who are not able to consent or who do not consent to participate (including linkage to clinical records) will not be included.
Facility inclusion criteria will be:

- Situated Gauteng province
- Follows national guidelines for viral load monitoring
- HIV positive patient burden≥ 30 per month

Participant inclusion criteria will be:

- Adult patients (>18 years)
- Not pregnant
- (Aim 1) Enrolled in HIV care at study site
- (Aim 2) Received HIV post-test counselling or adherence counselling

Participant exclusion criteria will be:

- Indicates they do not intend to receive HIV care at the study site *(Implementation note: this was operationalized as the absence of a clinical chart at the clinic.)*
- Requires acute medical care that would be hindered by participation in the study
- Determined by clinical staff not to be physically or emotionally able to initiate ART

- Is currently pregnant
- Does not speak one of the primary study languages: English, Zulu, Sotho, Xhosa
- Is not able to consent (e.g. intoxicated or of limited mental capacity)
- Does not consent to participate in the study, including linkage to clinical records for follow-up of the primary behavioral outcome (ART uptake and adherence over the first 6 months)

5.2.3. Intervention.

The U=U video intervention will be developed in Aim 1. The intervention will be piloted via three treatment modalities: (T1) controlled exposure, using the tablet-based app in the context of a survey; (T2) clinical exposure, in which patients will see the video in the clinic waiting room and will be exposed to the app during HIV counseling; and (T3) text message exposure, with monthly interactive messages.

5.2.3.1 Intervention assignment, period 1 (two study arms, n=45/arm)

Arm A vs. Arm B. During the first period of recruitment, patients completing HIV post-test or adherence counseling will be referred to study staff for recruitment (Fig 7). Patients will complete a brief intake survey. They will then be randomized 1:1 at the individual level to "no exposure" (Arm A, n=45) vs. "controlled exposure to the tablet-based video intervention" (Arm B, n=45). Arm B will then receive the intervention on tablet, delivered in the study interview setting. Respondents in Arms A and B will then complete additional questions, constituting the immediate post-test survey. Comparisons of outcomes in Arm A and Arm B will enable rigorous inferences on the effect of "controlled exposure" due to randomization.

~~*5.2.3.2 Intervention assignment, period 2 (third study arm, n=45):*~~

~~Arm C "clinical exposure". We will conduct a demonstration project to assess the feasibility and acceptability of delivering the U=U video intervention in real world clinical settings, rather than in a controlled study context. After period one enrolment has been completed at the three clinics, the intervention will be integrated into routine counseling procedures at each clinic. In collaboration with clinic leadership, HIV counselors will be trained to use the tablet-based U=U intervention to enhance TasP literacy as part of routine counseling and will be provided a tablet for the duration of the pilot. Additionally, the full video intervention will be shown on TVs in the clinic waiting rooms (on repeat, in rotation with other material). All patients receiving counseling at the study clinics after a specified implementation date will be considered "exposed" to the intervention. Patients completing counseling during this period will be referred to study staff for recruitment. Patients who provide consent (Arm C, n=45) will participate in the intake and immediate post-test surveys (Fig 7). Comparisons of Arm A and Arm C will enable inferences on the effect of "clinical exposure" to the intervention in a non-randomized pre/post design, comparing patients receiving counseling before and after the intervention at the same facility.~~

Implementation note: Arm C participants were reallocated to Arms A and B.

5.2.3.4 Text-message reinforcement.

Participants in intervention arms (B ~~and C~~) will additionally be sub-randomized 1:1 to receive six monthly interactive SMS/text messages (for simplicity, not shown in Fig 7) related to the U=U video content. Arm B participants will also receive the App on their phone (if they have a smart phone) and an information sheet, to enable them to continue to engage with the information and share with others.

Implementation note (added 7/30/2025): The six text messages were randomized to enable assessment of impact of different messages. Further, they were delivered on a set schedule (same day each month for all participants) and were not linked to participants next appointment dates. Thus, the text messages were intended to be additional doses of U=U information, not reminders of scheduled clinic visits.

5.2.4. Data collection.

For all study arms, data will be collected on participants via a brief intake survey, an immediate post-test survey conducted during the enrolment visit, a 6-month follow-up survey, and via linkage to clinical records. Fig 7 shows the order of data collection activities for the different study arms. The intake and immediate post-test surveys will be conducted in person on a tablet, with the assistance of a trained interviewer. Due to variable computer literacy in the study population, study staff will be available to assist with reading the survey questions and guiding the participant through the survey. The surveys will be implemented in English, Zulu, and Sotho and Xhosa three of the most widely spoken languages at public sector clinics in Gauteng and Xhosa and English being widely spoken in Western Cape Townships. The 6-month follow-up survey will be conducted in person or by phone for Aim 1 and Aim 2. In addition to these data collection activities, for Arms B and C, participant responses to questions embedded in the App-based intervention and responses to the randomized text messages will be logged.

Implementation note (added 7/30/2025): Six-month survey and Arm C were dropped as described above.

5.2.5. Outcomes and follow-up.

The primary goals of the pilot trial are to establish: (a) feasibility of the intervention and data collection methods; (b) acceptability of the intervention, and different video modules and delivery modalities; (c) effects on knowledge about the efficacy of TasP; (d) effects on attitudes towards ART as a prevention strategy (prevention motivation) and treatment strategy (treatment motivation); and (e) preliminary impact on ART uptake and adherence through six months, defined as the number of monthly ART medication pick-ups over the first six months after study enrolment, as measured in linked clinical records. Additionally, we seek to assess the extent to which effects are moderated by patient characteristics including: gender, age, relationship status, post-test vs. adherence counseling, and altruistic preferences.

5.2.5.1 Intake and immediate post-test survey.

The 10-min intake survey will collect basic information on patient demographics and potential moderators. The 25-min post-test survey will include the following domains (described in Aim 1): acceptability of the intervention (Arm B, C), beliefs about the health benefits of ART, beliefs about HIV transmission with / without ART, attitudes towards ART as a prevention strategy, HIV prevention altruism, internalized stigma, mental health, partnership status and towards disclosure, self-efficacy to take ART, barriers to adherence, and self-reported adherence and sexual risk behaviors.

~~*5.2.5.2 Six-month follow-up survey.*~~

~~The six-month follow-up survey will be conducted at the first scheduled clinic visit occurring after six months since enrolment. Once six months have elapsed, all participants will be contacted with a reminder of their next appointment at the clinic and with a reminder that the follow-up survey will be conducted at that visit. Patients will be given the option of participating in the follow-up survey on another date if more convenient, or by phone. All participants will be compensated for their time participating in the follow-up survey. We will attempt at least three contacts in order to retain respondents for the follow-up interview. The six-month follow-up survey will cover the same domains as the immediate post-test survey.~~

5.2.5.3. Exit interviews (n=30).

After the six-month follow-up, 30 participants in Arms B and C will be randomly selected to participate in a one-on-one, open-ended, key informant interview with study staff. Domains will include: acceptability of the intervention; understanding of information provided; how if at all the intervention affected how they think about ARVs, condoms, sex, and relationships; whether they have talked about TasP with others; and any challenges they have faced due to the intervention. Interviews will be audio recorded, transcribed, translated, and analyzed using a grounded theory approach.[80] Counselors will also be interviewed to gain their qualitative perspective on the acceptability and feasibility of the intervention.

5.2.5.4. Linkage to clinical records for primary behavioral endpoints.

To assess preliminary impact and to demonstrate feasibility of measuring clinical endpoints, we will link (with consent) to clinical records for six months after study enrolment. Our primary behavioral outcome will be ART uptake and adherence through six months, defined as the number of monthly ART medication disbursements occurring over the six months following study enrolment. Current protocols specify monthly medication pick-ups. Patients may have fewer than six visits if: they did not initiate ART, they delayed initiating ART, they started ART but missed medication pick-ups, or they started but were not retained on ART (or transferred out). Thus, our measure is designed to capture in a single outcome a range of behaviors related to ART uptake and adherence. Because some clinics have moved to same-day ART, we have defined this outcome to be valid regardless of when ART is started. Additionally, the composite measure is likely to have greater power than the individual component measures. As secondary outcomes we will additionally assess ART uptake within 30 days and retention in care at six months, defined as being no more than 30 days late for scheduled clinic visit closest to six months.

We will also assess documented viral suppression at six months. Guidelines specify that a viral load should be conducted at six months after ART initiation. Because patients may take several weeks to initiate ART after diagnosis and because many patients do not get their VL precisely at six months, we will allow for a ten-month window after study enrolment. With consent, we will extract VLs from clinical charts as well as the national laboratory database, enabling us to trace patients who may have transferred to other clinics. We will define suppression as VL<50 copies. We will assess monitoring (regardless of suppression) as a secondary outcome.

Note (added 7/30/2025): changes in behavioral endpoints are described above. Documented VL<200 copies/ml at 3-10 mo was defined as the primary endpoint (due to changes in VL testing guidelines & practices in the middle of the study). Retention measures were adjusted due to missing data on dates of next appointment and variation in 1 vs 2-month ART dispensing.

5.2.6. Data Analysis.

Acceptability will be assessed at immediate post-test with respect to “ease of use” and “usefulness” for intervention study arms (B and C). The intervention will be determined “acceptable” in different subgroups (by moderating variables) if average Likert scores are 3 (out of 4) or higher. We will also assess acceptability, clarity, and salience of specific video modules through embedded questions and rankings in the tablet-based intervention and assessing which were watched again. Other study endpoints will be knowledge and attitudes related to TasP, internalized stigma and mental health, and HIV prevention altruism at immediate post-test and 6 months, and ART uptake and adherence and viral suppression assessed in clinical records. Effects on these endpoints will be assessed through comparisons of study arms. We will conduct separate analyses comparing Arm A (“no exposure”) vs Arm B (randomized “controlled exposure”), comparing Arm A (“no exposure”) vs Arm C (non-randomized “clinical exposure”), and comparing randomized monthly “text messages” vs. “no text messages” in Arms B and C. For each analysis, treatment arms will be compared across pre-treatment characteristics to assess balance. To evaluate impact, we will compare means for all outcomes across treatment arms using simple linear regression with robust standard errors, adjusting for clinic and type of counselling (stratifying variables). For binary outcomes, we will use logistic regression and estimate marginal effects (risk differences). As a sensitivity analysis, we will adjust for pre-treatment characteristics on the intake survey that are substantially imbalanced ($p<0.1$) and which are thought to be correlated with ART adherence. The trial will be analyzed on an intention-to-treat basis. Every effort will be made to follow up patients for the six-month follow-up survey. Missingness, if >10%, will be addressed via the inverse probability of censoring weights (IPCW). In addition to the “main effects” analyses described, we will assess interactions by theory-driven moderating variables e.g.: counselling type, baseline relationship status, and general altruism.

5.2.7. Sex as a biological variable.

Women and men may engage with the issues surrounding U=U in different ways. We will recruit both men and women to the pilot study. We will assess for gender-specific barriers and facilitators in our qualitative data collection, and we will assess intervention impacts separately by gender. We note that due to the small sample size of this pilot, our primary analyses will pool men and women.

5.2.8. Power.

Our pilot study is powered to detect clinically significant impacts on U=U knowledge and attitudes. In preliminary data, we found that Gauteng university students (n=363) perceived virally-suppressive ART reduced transmission risk by an average of 20% (s.d. 25%). (The actual reduction in risk is at least 96%.) A successful intervention would substantially increase perceived efficacy of ART in reducing transmission. With 45 control participants and 45 treated participants per arm, we are powered at 97% to detect at least a 2-fold increase in perceived efficacy of TasP, from 20% to 40%. This pilot is not powered for impact on behaviors.

5.2.9. Scientific rigor of the approach to Aim 2.

Aim 2 will establish feasibility and acceptability of delivering U=U information via video in "controlled" and "clinical" settings, and will assess effects on knowledge, attitudes, and preliminary impact on ART adherence in a pilot trial. The approach is scientifically rigorous because:

a) We will evaluate the "controlled exposure" intervention in a randomized trial, ensuring high internal validity.

b) We will assess feasibility and acceptability of clinic-level integration of the intervention into routine HIV counseling, the delivery modality most likely to be scaled up and the approach to be tested in a future R01.

c) We will evaluate impact with respect to theory-driven, validated measures of intervention acceptability, TasP knowledge and attitudes, HIV prevention altruism, and internalized stigma, which we will pre-test in Aim 1.

e) We will establish feasibility of collecting data on behavioral impact through linkage to patient charts.

f) The study is appropriately powered for a pilot trial that will establish convincing evidence of intervention acceptability and preliminary impact, which can be further tested in a larger scale trial in a future R01.

6. Data management and storage

Data with patient identifiers (i.e. names, addresses) will be stored at HE^{2}RO on a password-protected server, as described below.

- **HE2RO Server Location**. Data stored by HE^{2}RO is located on an access-controlled local server in the HE^{2}RO office block. This server is physically secured in an access-controlled room, and only accessible virtually by designated persons with HE^{2}RO domain login credentials.

- **HE2RO Server Details.** The HE^{2}RO server is running the Windows Server Standard Core 2019 Operating System. As the server is the HE^{2}RO network domain controller, Microsoft Active Directories is used to manage user accounts and folder permissions. Access to data storage folders on the server require an active HE^{2}RO domain user account. User access to folders are decided on a case-by case basis, and limited appropriately. Remote access is controlled by means of a Virtual Private Network (using Forticlient or OpenVPN VPN software), which also requires HE^{2}RO domain login credentials.

- **HE2RO Server Backup and Maintenance.** The server is secured and maintained by the HE^{2}RO IT service provider, who conduct checks on server hardware and security on a regular basis, and who is also responsible for backing up the HE^{2}RO server onsite daily, and offsite on a weekly basis.

All analyses will be conducted on fully anonymized datasets. These fully anonymized datasets will exclude all specimen and record identifiers. Instead, they will have a random study ID. The fully anonymized dataset will be made available to study staff at BU for the analyses planned in this proposal.

HE2RO will retain a linking file with data on participant identifiers (name, surname, national identification number) and TIER.Net record identifiers, which will be used in linking the questionnaire and medical records. The key linking the random study ID to the specimen and record identifiers will be held on the HE2RO password-protected server with access restricted to the PIs and server administrator. HE2RO will not have a crosswalk linking these specimen and record identifiers to patient identifying information.

7. Ethical Considerations

7.1. Information sheet and consent form

Upon completion of eligibility screening, the study interviewer will complete the informed consent process. The interviewer will use the information sheet to describe the study in detail, answer any questions that participants might have, as well as work through a standardized Question and Answer information supplement. Once all questions have been answered, the consent process will be documented on the signed consent form. The information sheet and consent form for our study describes the nature goals and procedures of the study. The consent form will be administered by a trained study staff member in English, Sotho, Zulu and Xhosa(depending on the participant's preference). The information sheet will explain that if participants choose to be in the study they will be asked to complete a questionnaire. Participants will be assured that data collected for our study will be kept strictly confidential. They will be told that participation in the study is completely voluntary.

This documentation will be left with participants and will include the contact details of the Principal Investigator, the Project Director and the Chair of the Wits HREC, should they wish to contact the study team or lodge a complaint. If participants are illiterate, they will be asked to bring in another person who can read who will witness the consent process. The third party will sign the consent form, and the illiterate participant will mark the consent form.

7.2. Potential Risks

We believe that our study poses no physical risks to subjects beyond those routinely encountered. It may, however, pose risks associated with breach of confidentiality and disclosure of HIV status.

Loss to HIV care

The proposed research aims to increase uptake of HIV treatment and to reduce losses in the HIV care cascade. To do so, we will provide key information on the prevention benefits of ART through an educational video intervention. Although we anticipate that providing information on U=U will increase uptake and adherence to ART, there is a risk, however small, that patients who receive this intervention will start and stay on ART at a lower rate.

Breach of confidentiality

A potential risk of the study concerns the confidentiality of data about HIV status and treatment program enrollment. A high level of stigmatization continues to inhibit the disclosure of HIV status in the study population. Data collected in surveys or clinic records could be disclosed and reveal a person's HIV status. There is always the possibility of a breach of confidentiality when conducting research. While this is acknowledged, there is very low likelihood because of the precautions that will be taken to protect confidentiality.

Unintended behavioral consequences

There is a risk that providing individuals with information on treatment-as-prevention will lead to risk compensation behaviors and elevated rates of unprotected sex as individuals (accurately) perceive lower risks of HIV transmission from unprotected sex with partners on ART. Such behavior could lead to increased exposure to – and transmission of – other sexually transmitted infections, and to unintended transmission of HIV if people with HIV do not adhere to ART and are not virally suppressed. Clear and accurate information on these risks will be provided. These risks will be mitigated by providing carefully crafted counseling messages as described below. While these are real risks, the risks of NOT providing information on ART as a technology to reduce HIV transmission risk are very large, given the large share of HIV-infected people not yet on ARVs who continue to have unprotected sex (as discussed in the Research Strategy section). Data on self-reported ART adherence and sexual behavior will be collected at baseline and 6-months follow-up to assess potential adverse consequences.

Emotional distress

The study population for this study will be patients who receiving HIV counseling as part of standard of care. These patients include those who have been newly diagnosed with HIV as well as patients who are receiving adherence counseling. Though unlikely, it is possible that information presented on U=U may cause some emotional distress for some potential subjects. The intervention will be implemented in coordination with HIV counselors at public sector

clinics. These counselors are trained to identify and support patients in emotional distress. Patients who counselors identify as being in emotional distress will not be referred to the study. Further, study participants who experience emotional distress during the survey will be referred to the HIV counselors on site for support.

7.3. Protection against risks

Loss from HIV care

The study clinics that we will work with have routine procedures to conduct outreach to patients who are lost from HIV care through a team of counselors. As our study follow-up period for our primary behavioral outcome is only 6 months and consists entirely of passive follow-up, we will not interfere with nor further supplement standard of care regarding patient outreach during the first 6 months. When we approach patients for the 6 month follow-up survey, those patients who do not come to their 6-month visit will be tracked and contacted at least 3 times for purposes of study retention. We will encourage study participants – including those that have disengaged from care – to return to the clinic to participate in the survey in person. When they come for the follow-up interview, they will be referred to clinic personnel to offer re-engagement in care per normal clinic protocols. Participants who choose not to return to the clinic will be offered a phone interview.

To protect against the risk that our TasP educational video intervention inadvertently discourages patients from remaining in care, we will develop the intervention with the guidance of an Intervention Mapping Working Group including participation from people with HIV, clinicians, HIV counselors, and experts on health communication and clinical HIV care. We will pre-test the intervention extensively (Aim 1) before implementing it in clinical settings (Aim 2).

Breach of confidentiality

Subject confidentiality is essential to the protection of human subjects and to getting accurate information for this study. We will train our study team to respect subject confidentiality in multiple ways. First, they will be trained in maintaining confidentiality at the HIV treatment clinic when potential subjects are recruited, consented, and administered questionnaires. Second, we will maintain the confidentiality of all records collected for this study.

Steps taken to ensure that the HIV status of participants remain confidential and therefore minimize the risks associated with potential HIV-related stigma for individuals participating in the research will include:

(i) Confidentiality of HIV status maintained by the research staff

(ii) Participants will be referred to resources to support disclosure and to help individuals decide how, when, and to whom to disclose.

(iii) All research staff will be trained to manage adverse reactions experienced by participants during disclosure, and there will be clear pathways for referral

(iv) It will be made clear in the study information sheet and during the consent process at enrolment, that participation in the study is voluntary, that participants can withdraw from the study at any time, without compromising the care and support they could receive, and that data collected will be stored in a confidential manner.

(v) The Wits Research Ethics committee includes a local representative from the proposed study area whom participants can contact directly if they have concerns about the study.

Emotional distress

A small risk of psychological distress may be posed by study questions regarding family communication, relationships, disclosure and dealing with HIV/AIDS which may evoke unpleasant feelings during administration of the counselling intervention or during completion of the study questionnaire. Given that participants may find answering questions about these issues upsetting, they will be asked in as sensitive a manner as possible. If a participant experiences emotional upset during the interview, the research staff will use their extensive training to handle these situations and refer participants to the clinic-based lay HIV counsellors for further support if needed.

We will also remind participants that they can terminate the interview at any time. There is also the risk of fatigue from interviewing. To deal with this, regular breaks will be encouraged.

To further maintain confidentiality, all statistical analyses of the study results will be presented in aggregate in any technical reports or in manuscripts submitted for publication in scientific journals. Upon completion of the study, computer files and any data collection forms containing study data will be retained for five years and then destroyed.

Unintended behavioral consequences

To mitigate against adverse consequences resulting from possible risk compensation behaviors:

a) We will develop the intervention with the guidance of an Intervention Mapping Working Group including participation from people with HIV, clinicians, HIV counselors, and experts on health communication and clinical HIV care, as well as consultation with representatives of the Department of Health.

b) We will pre-test the intervention extensively (Aim 1) before implementing it in clinical settings (Aim 2) to ensure that the key message is accurately conveyed to participants that treatment-as-prevention does not protect against the risks of STI infection and transmission, nor pregnancy. The app will also inform patients about STI and pregnancy services.

c) We will pre-test the intervention extensively (Aim 1) before implementing it in clinical settings (Aim 2) to ensure that the key message is accurately conveyed to participants that the effectiveness of treatment-as-prevention depends on viral suppression, and that daily adherence and routine viral monitoring are essential to ensure viral suppression. The app will encourage participants to inquire about their VL during clinic visits and to keep their VL appointments.

d) We will select clinics that follow national guidelines for viral monitoring, which specify a VL six months after starting therapy, and which provide screening, counseling, and treatment for other STIs,

e) At the study clinics we will train HIV counselors on the benefits and risks of U=U as well as the importance of viral load monitoring, the importance of couples counseling and testing, and on the importance of STI and pregnancy screening.

f) Although we are not powered in this pilot study to assess incidence of STIs or pregnancy, we will assess beliefs about protection against other STIs and pregnancy as well as self-reported behaviors related to ART adherence and condomless sex at immediate post-test and at 6 months follow-up.

g) Finally, although we have detailed the many ways that we will mitigate risks of adverse impact, we also stress that the risks of NOT providing information on ART as a technology to reduce transmission risk are very large, given the large proportion of HIV-infected people not yet on ART who continue to have condomless sex (as discussed in the Research Strategy section) and the large proportion of HIV-infected people who choose not to start or adhere to ART – particularly among young adults. We believe the potential benefits far outweigh the potential risks.

7.4. Potential benefits of the proposed research to human subjects and others

There will be no direct benefits to study subjects. However, we anticipate that this study will generate substantial indirect benefits to the subjects. The research we will undertake is expected to generate information about the national HIV care and treatment program that will allow for improvements to the program. The results of the study may thus lead to improvements in HIV care and keep patients alive and in care longer.

7.5. Participant cost and payments

Besides the time taken for informed consent decisions, subjects incur some time costs to respond to the questionnaire. However, we anticipate that the questionnaires should take no more than 45 minutes to administer. A small stipend (R150 ~ US$9) in total will be paid to participants in appreciation for their time completing the survey and participating in the video intervention. The stipend will be paid in two parts R100 at the end of the baseline study procedures and a R50 will be paid after completion of the follow-up survey.

7.6. Importance of the knowledge to be gained

U=U campaigns have now been implemented in nearly 100 countries. However, U=U is not integrated into routine HIV counseling in South Africa and our preliminary data from multiple populations (rural KwaZulu-Natal, urban

Gauteng) indicate that young adults in the general public are not aware of the prevention benefits of ART. There is little rigorous evidence on how best to share information on U=U and what impact disseminating U=U information will have on the health and wellbeing of PLWH.

The knowledge to be generated by this study will inform how best to provide information on U=U in the context of HIV post-test and adherence counseling in public sector clinics in South Africa. The follow-on R01 will then determine the impact of providing this information on health outcomes. This study will address an important gap in the current scientific knowledge around how to disseminate information on the prevention benefits of ART. As explained in the previous section, we believe that the risk to subjects in our study is minimal and is outweighed by the indirect benefits and the potential importance of the findings.

8. Data and Safety Monitoring Plan

This project will be managed out of the offices of the Health Economic and Epidemiology Research Office (HE2RO). The study will be managed through regular project team meetings to discuss progress, problems with enrolment and data collection, data quality and ethical issues. Study accrual will be monitored by discussions with the study staff and review of study forms.

All participants will be assigned a four-digit study identification number. All data will be collected using a data collection software on electronic tablets, exported and stored in a password controlled STATA database. Data from the medical records reviews will be entered on tablets on site onto an electronic follow-up form by study data collectors.

The data collection documents will be coded and all documents with participant identifiers on them will be stored separately either in a locked cabinet for paper documents or a password controlled electronic file with access limited to the study team. Identifying information will be collected in a linking document that will connect questionnaire data and medical records review data. The analytic dataset will be stripped of all identifying information. As noted above, linking files will be stored in an access controlled cabinet. The linking file will be kept until all data collection is complete and all data has been linked. Once the linking is complete, the linking file will be destroyed.

All reconciled data files will be electronically transferred to Dr Dorina Onoya on a daily basis. The database will be password protected with access limited to the members of the study team. The electronic data will be converted to SAS, STATA or SPSS for data analysis. All databases will be password protected with access restricted to the members of the study team. HE2RO has a dedicated appliance firewall that only allows access to computers internal to HE2RO. Therefore, only HE2RO staff with log-in credentials will have access to the particular folder that will contain the data.

All hard copies of consent forms will then be stored in a locked cabinet in the study office with only the study team having access to the data. The HE2RO field office is locked when not in use. All hard copies of study documents and interview digital records will be transferred to the HE2RO offices for long-term storage. All data will be destroyed five years after the date the studies are closed with the IRBs.

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