The effect of undetectable equals untransmittable (U=U) messaging on HIV testing uptake among South African men: a randomized trial.

[Short title: U=U]

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Question:	Can messaging about being undetectable equals untransmittable (U=U) increase HIV testing uptake in men?
Purpose:	HIV testing is the gateway to HIV prevention, treatment and HIV control, but uptake is suboptimal in South African men. Consequently, men have poor HIV outcomes including lower HIV testing uptake, lower ART initiation and a lower proportion achieving viral suppression. This study will investigate the effect of participatory, user-designed messaging to increase knowledge about U=U on HIV testing uptake in men in the Klipfontein Mitchells Plain (KMP) district in Cape Town, through a randomized trial design.
Primary objectives:	1) To develop U=U messaging that encourages HIV testing uptake in men using a participatory, user-centered design. Messaging will seek to assuage the fears of testing HIV positive by conveying the message that HIV treatment makes it possible for HIV positive people to be untransmittable and to live normal lives. 2) To investigate the effect of U=U messaging on HIV testing uptake in men compared with the standard of care messaging.
Design:	The study will be conducted in two phases: Phase 1 is a participatory, human-centered design framework that will be used to develop U=U messages to increase HIV testing uptake in men. Phase 2 is a cluster randomized trial that will determine the effect of U=U messaging on HIV testing uptake. Men in the intervention group will receive invitation cards for mobile HIV testing that contain U=U messages. Men in the control group will receive invitation cards for mobile HIV testing that contain standard messaging. Mobile clinic days (i.e. clusters of men receiving invitation cards at one site on one day) will be the unit of randomization. The primary outcome will be HIV testing uptake at a community-based mobile clinic. Secondary outcomes will include the proportion of males tested who are HIV-positive and newly HIV positive.
Study setting and population:	KMP is a resource-limited, densely populated, high HIV disease burden area in Cape Town, where the use of health services among men is sub-optimal. Recruitment will be conducted by trained mobile clinic staff at high foot-traffic sites in the KMP community. Recruitment efforts will focus on young men in multiple mobile testing sites that are located in areas within KMP where there is a high burden of HIV.
Study size:	In phase 1, approximately 20 men will be invited to participate in formative research through insight workshops for U=U message development. After the initial message development, about 20 more men will be invited to give feedback and suggest improvements to ensure understanding and acceptability of the messaging. In phase 2, 40 clinic days will be randomized to intervention or control, with 100 men in the vicinity of the Tutu Tester receiving invitation cards for testing on each day (N=4,000).
Process:	In phase 1, mobile clinic staff will invite men to participate in an insight workshop at a community location. Men who agree to participate will respond to questions and take part in group brainstorming activities that will inform development of U=U messaging.

	The research team will map the ideas and themes and use these to create an invitation to men. Their feedback will be used to calibrate the messages for the phase 2 trial. In phase 2, a trained recruiter will deliver a U=U invitation message on intervention days and standard HIV testing messaging on control days to encourage HIV testing at a mobile clinic. On each day, recruiters will deliver about 100 invitation cards to young men in the vicinity of the mobile testing van where free HIV testing will be available.
Duration:	Phase 1 will run for one month. Phase 2 will run for 3 months.
Analysis:	In phase 1, acceptability will be measured through workshop feedback. In phase 2, a chi-squared test will estimate the effect of U=U messaging on HIV testing uptake compared with standard of care. We will also compare HIV positivity by study arm. Logistic regression analysis will model the effects of participant demographics, binary line of sight of mobile clinic, and time of day on testing uptake and time to presentation at the clinic.
Abstract:	HIV testing is the gateway to HIV prevention, treatment and HIV control, but uptake is suboptimal in South African men. Consequently, men have poor HIV outcomes including lower HIV testing uptake, lower ART initiation and a lower proportion achieving viral suppression. This study will investigate the effect of participatory, user-designed messaging to increase knowledge about U=U on HIV testing uptake in men in a high HIV disease burden area in Cape Town, through a clustered experimental design. This project has two main objectives. The first is to develop a U=U message that encourages HIV testing uptake in men using a participatory, user-centered workshops. Messages will seek to assuage the fears of testing HIV positive by conveying the message that HIV treatment makes it possible for HIV positive people to be untransmittable and to live normal lives. Second, the study will investigate the effect of U=U messaging on HIV testing uptake in men compared with the standard of care messaging. This study will utilize the DTHF Tutu Tester program, a mobile HIV clinic, to trial this new messaging intervention.

1. Introduction

South African men have suboptimal levels of HIV testing, antiretroviral therapy (ART) initiation, retention and survival on treatment and have poorer HIV outcomes than their female counterparts, suggesting that these men remain underserved in the context of the HIV response (Cornell, Cox, & Wilkinson, 2015; Cornell et al., 2012; Cornell & Myer, 2013; Johnson et al., 2017). Only 78% of men living with HIV know their status, 67% of those men are on ART and 82% were virally suppressed in 2017 (HSRC, 2018). While the increased focus on key populations, pediatrics, girls and young women has produced a better understanding of their sexual health needs and improved HIV related outcomes (Haal, Smith, & van Doorslaer, 2018), the needs of men in South Africa remain understudied.

ART-based interventions have consistent efficacy and effectiveness data and represent the standard of care for both HIV prevention and treatment in recommendations by UNAIDS, WHO, and the Ministry of Health in South Africa (Bekker et al., 2016; Meintjes et al., 2017). Taking daily ART eliminates enough of the virus so that HIV cannot be detected via viral load testing (Eisinger, Dieffenbach, & Fauci, 2019). Those who have an undetectable viral load cannot transmit the virus to sexual partners or through giving birth (Davies et al., 2018; Eisinger et al., 2019), commonly referred to as U=U (undetectable viral load equals untransmittable virus). Typical communication about and delivery of HIV testing and ART in South Africa has primarily focused on "access" (Sharma, Barnabas, & Celum, 2017) as opposed to promoting uptake and adherence as a rewarding experience. U=U is a message that promotes the reward of knowing one's status (peace of mind) and starting on treatment if diagnosed with HIV to remain healthy and alleviate the stress of HIV transmission to sex partners. The U=U message has been effectively promoted in Europe and North America where people living with HIV describe feeling free of internal and external stigma as a result (The Lancet HIV, 2017). However, awareness of the large prevention effects of ART remains low in many parts of sub-Saharan Africa. Recent studies have shown that many men are unaware that ART can dramatically reduce the likelihood of HIV transmission.

While ART-based interventions are efficacious, the ongoing adverse outcomes among men suggest implementation challenges, including adoption and adherence. Findings from implementation research have recommended differentiated services, focused on dedicated testing and treatment programs tailored to the needs of men, to improve care outcomes (Fakoya, Dybul, & Sands, 2019; Sharma et al., 2017). Yet, there are few rigorous evaluations on the impact of services targeting men, particularly in HIV endemic, low- and middle-income countries.

The behavioral economics (BE) health model (Rice, 2013) suggests that the context in which decisions are made influence those decisions. Health messaging frequently fails to adequately influence behavior because it appeals to dread, which can thwart adaptive health-seeking behavior and lead to vulnerability denial instead (Arndt & Goldenberg, 2017; Millar & Millar, 1995). The BE health model proposes reframing the message to align with desirable outcomes, which eases the decision making context (Rice, 2013). By reframing the message to align with reward-seeking behavior instead of disease detection, the decision and resultant behavior is simplified. Since the U=U message complements this theoretical framework, the overarching goal of the proposed project is to design and adapt a U=U message and to describe its impact on improving HIV testing uptake among men 15 to 39 years old in a high HIV disease burden community in Cape Town, South Africa.

2. Methods

2.1. Objectives – HIV testing is the gateway to HIV prevention, treatment and HIV control, but uptake is suboptimal in South African men. Consequently, men have poor HIV outcomes including lower HIV testing uptake, lower ART initiation and a lower proportion achieving viral suppression. This study will investigate the effect of a participatory, user designed message to increase knowledge about U=U on HIV testing uptake in men in the Klipfontein Mitchells Plain (KMP) district in Cape Town, through a randomized trial design. The primary objectives of this study are 1) to develop a U=U message that encourages HIV testing uptake in men using a participatory, user-centered workshop, and 2) to investigate the effect of U=U messaging on HIV uptake in men. The primary outcome will be HIV testing uptake at a community-based mobile clinic. Secondary outcomes will include the proportion of males tested who are HIV-positive (and newly HIV positive).

2.2. Study Duration and Setting – The study will be 12 months in duration including the preparation period, Phase 1, Phase 2 and analysis. The study will take place in KMP, a resource-limited, densely populated, high HIV disease burden area in Cape Town, where the use of health services among men is sub-optimal. The DTHF Tutu Tester offers mobile HIV testing clinic days in various locations in the region, including KMP. Trained recruiters stationed at the Tutu Tester mobile clinic sites distribute invitation cards inviting men to visit the mobile clinic for a voluntary HIV test. The intervention will utilize the Tutu Tester to trial a new messaging intervention. DTHF will build upon their existing activities and relationship with the local community to implement this study in KMP. DTHF will complete all data collection. Penn will not take part in data collection, nor will Penn interact with the subjects.

2.3 Inclusion criteria and recruitment – Recruitment will be conducted by trained mobile clinic staff at selected high foot-traffic sites in the KMP community. Men in high HIV disease burden areas in KMP will also be recruited through community outreach activities to participate in the study. Inclusion criteria for the study will be males at least 18 years of age within the vicinity of the mobile Tutu Tester HIV testing van.
The study will consist of two phases:

2.4. Phase 1

2.4.a. Design – In phase 1, we will develop a U=U message using a participatory, human-centered design framework. There is increasing recognition that intervention design should incorporate viewpoints from the target audience to enhance collaboration, improve acceptability, and increase uptake (Byrne & Sahay, 2007; Mabunda, Khoza, Van den Borne, & Lebese, 2016). Thus, this participatory research will include workshops of approximately 40 men from a population that may potentially be recipients of the intervention.

2.4.b Process – Mobile clinic staff will invite approximately 20 men from high traffic locations in the KMP region to participate in design workshops for the development of a U=U message, that even if HIV positive they can be untransmittable, to normalize HIV and mitigate the fears of testing HIV positive. Each workshop participant will be asked to give informed consent, and then a trained facilitator will present the U=U message to the participants and facilitate the group to develop a message that resonates with them in language that is sufficiently colloquial to enable easy understanding among local

men. Their suggestions and statements will be recorded in written form verbatim and used to generate the invitation message. Once developed, the message will be presented to approximately 5-10 more men from within the community who will be invited to rate and suggest improvements to the acceptability of the prototype message. Following this exercise, the message will be fine-tuned and the final message will be printed on invitation cards for the phase 2 randomized trial.

2.5. Phase 2

2.5.a. Design – In phase 2, a cluster randomized trial will be conducted to determine the effect of the U=U message on HIV testing uptake. Individual mobile clinic days (i.e., the tester being parked at one site for one day) will serve as the unit of randomization, with each site day being assigned to the treatment or control condition via a computer-generated randomization process. Randomization will be stratified by testing location so that an equal number of clinic days at each location within KMP are assigned to each study group. On each mobile clinic day during the study, men in the vicinity of the mobile clinic will be offered invitation cards for same-day testing. Invitation cards will have unique identification codes. The information content on the referral cards and the mobilization approach will vary depending on condition.

2.5.b. Intervention group – Following phase 1, the final U=U messages will be printed on invitation cards to be distributed at mobile testing sites. Messages will seek to assuage the fears of testing HIV positive by conveying the message that HIV treatment makes it possible for HIV positive people to be untransmittable and to live normal lives. Messages will encourage men to come in for HIV testing at the mobile clinic on the same day. A mobile clinic recruiter will deliver the invitation and share a brief script explaining U=U.

2.5.c. Control group – The standard invitation cards used at the Tutu Tester contain basic information encouraging HIV testing. Messages will encourage men to come in for HIV testing at the mobile clinic on the same day. A mobile clinic recruiter will deliver the invitation and share a brief script including the standard Tutu Tester message.

2.5.d. Study Instruments: Invitation cards – After mobile clinic recruiters deliver the invitation card and scripted verbal message, they will request the participant bring the card with them if they return to test. The card will contain the distribution date and time and recruiter information. The recruiter will also separately record the date and time the invitation was delivered, and whether the mobile clinic was visible on the card. When the participant returns to visit the mobile clinic, the recruiter will request the card and record the date and time of presentation as well as the unique identification code on the card. The participant will then be invited by a counsellor into a cubicle in the mobile clinic to complete a rapid HIV test after the counsellor consents the participant.

2.5.e. Study Instruments: Questionnaire – Key information will be collected from participants who come for testing via tablet. This intake will be completed immediately after an individual arrives at the Tutu Tester and presents their card. This will include a confirmation of inclusion criteria to ensure that the men are at least 18 years old. Other key information will include: type of message (intervention or control), line of sight, date and time of message delivery, date and time of presentation for HIV testing,

time taken to get tested, age, whether the participant brought a peer or partner, whether the person stayed for an HIV test or not and HIV status. Several open-ended questions to learn about men's perceptions of the U=U messaging may also be asked including: if they had any previous understanding of U=U, what they think about the message and how this might change their behavior. The DTHF team will translate and validate the questionnaire and confirm its cultural appropriateness. As per standard operating procedure, those who test HIV positive will receive post-test counselling and assessment by a nurse and will be referred to their preferred clinic facility for HIV treatment.

2.5.f. Sample size and power calculations – In phase 2, the DTHF Tutu Tester will circulate between approximately four different locations within KMP. The Tutu Tester will be based in only one location on any given day. Clusters will comprise men who receive invitation cards on the same clinic day. Power calculations assumed 8 percent HIV testing uptake among men in the control group (based on two operational pilots conducted by our team) and an intraclass correlation of 0.02. With 40 clinic days in the study and 100 men within the vicinity of the Tutu Tester receiving invitation cards on each clinic day, we will have 80 percent power to detect a difference in HIV testing between groups of at least 5 percentage points.

2.5.g. Outcomes and analysis – The primary outcome will be HIV testing uptake, measured at the Tutu Tester based on presentation of the invitation cards. A chi-squared test will be conducted to estimate the effect of the intervention on HIV testing uptake. Logistic regression models will also be estimated to control for location, time of day, and distributor effects. Additional outcomes examined will include the proportion of males tested who are HIV-positive (and newly HIV positive).

3. Protection of Human Subjects

3.1. Ethics – The study will be reviewed and approved by the University of Cape Town Health Science Research Ethics Committee (HREC). The protocol meets the Common Rule criteria as the research study is expected to pose no more than minimal risk to subjects AND the procedures fall within "category 7" outlined by the Office for Human Research Protections (OHRP) and in compliance with 45 CFR 46.110(b)(1). Our research focuses on assessing the uptake of HIV testing at a mobile clinic. The overall methodology of the protocol is the employment of workshops and a randomized trial of two HIV testing invitations. This type of behavioral study is best grouped or otherwise described as being "category 7" using the OHRP designation system. There are support services for participants at the site, including staff who are able to counsel participants on site, or telephonically, as well as established referrals to external counselling resources. Participation in the study is voluntary.

Participants who present for an HIV test will sign individual voluntary written informed consent form before enrolling. This consent will invite them to participate in the study, complete the questionnaire and complete an HIV test. Each participant will have time to ask any questions or raise any concerns they might have. Participants may refuse participation, which will not affect further treatment and any reasons for non-participation will be recorded. Participants will have the option to choose not to participate in the study at any time. All information is anonymous and will be kept confidential. The name of investigators who are responsible for conducting the study and direct contact details (telephone, address, e-mail) will be made available on the informed consent forms. The Site Investigator or designee will maintain, and store securely,

complete, accurate, and current study records throughout the study, in accordance with local regulations. All records will be stored for five years from the beginning of the study.

3.2. Risks – There are minimal risks to study participants. The primary risks involved in study participation are inadvertent loss of confidentiality. Procedures will be implemented to ensure maintenance of privacy, confidentiality, and security of the data obtained. Although the study site will make every effort to protect participant privacy and confidentiality, including conducting interviews in a private space, it is possible that participants' involvement in the study could become known to others. Social harms will be monitored and documented throughout the duration of the study. Should additional support be required for some participants due to study-related harms, referrals will be made to community-based services as needed.

3.3 Benefits – Participants will benefit from the hearing a U=U message adapted for the context. Participants and others may benefit in the future from information learned from this study. Participants may appreciate the opportunity to collaboratively contribute to the field of HIV research. Information learned in this study may lead to the development of effective messaging interventions to prevent onward HIV transmission in an HIV endemic community. Participants who test HIV positive will be referred to the nearest clinic for rapid ART start. We will follow up participants to ensure they seek referral and start ART.

3.4. Study Discontinuation – The study may be discontinued at any time by DTHF and/or the local Ethics Committees, as part of their duties to ensure that study participants are protected.

3.5. Data Security, Storage and Management – Information about study subjects will be kept confidential and all men who choose to participate will complete an informed consent form. DTHF and UPenn will jointly create standard operating procedures for electronic and paper data security and confidentiality procedures at collection, transfer, entry and storage levels, and will only release this information to study team members who have IRB approval. All study data will remain securely stored by DTHF for the duration of the study. University of Pennsylvania investigators and managers listed on the UPenn IRB application will have access to de-identified data only. No participant identifiers will included on any data forms; names and signatures will only be on the consent forms, which will be kept under lock and key by the DTHF study. At the end of the study, data will be kept for up to 5 years for electronic version, and up to 2 years for paper forms, including consent forms at the DTHF office.

3.6. Resources Necessary for Human Research Protection – The DTHF Tutu Tester will utilize their staff of trained recruiters to implement the study. No data collection will occur prior to appropriate human subjects training sessions and competency assessments of all involved research staff. UPenn and DTHF will work jointly to ensure that available resources, including funding and timeline, are commensurate with research objectives. Not only does UPenn have excellent facilities for research, but DTHF has a positive track record of conducting rigorous evaluations in South Africa.

4. Limitations

Stigma and denial remain significant problems in HIV endemic communities in South Africa. People are often willing to receive STI tests and screens as well as testing and screening for other chronic health conditions. However, people are less inclined to test for illnesses associated with death because of the possible

implications, that is, finding out that one is dying. Counterintuitively, discovering that one has a potentially life-threatening condition may actually save one's life because of the medico-technical advances aimed at intervening in life threatening situations. The medico-technological advancements help people to live full and healthy lives where in decades previous, they would have faced significantly reduced life expectancy. Tailored messaging aimed at supporting desirable outcomes may circumvent the stigma and denial associated with testing and initiating ART. The sampling of the study is biased because the mobile clinic actively targets men in high disease burden communities in Cape Town. Furthermore, while the services are provided in communities with high HIV prevalence, it is difficult to access those who chronically avoid diagnostic services, or who are unwilling to acknowledge their risk. It's possible that this intervention will not reach the most vulnerable men, given these access behaviors and therefore be somewhat biased as a result. However, the mobile clinic was developed in response to men's recommendations to increase access and acceptability of sexual health services for men.

5. Conclusion

Reversing and eradicating the HIV epidemic is dependent upon a treatment cascade that identifies and tests at-risk populations, linkage into care, adherence to treatment and consequent undetectable viral loads. If U=U messaging increases HIV testing over standard messaging, U=U should be used as part of a multi-pronged intervention package to improve men's entry into the prevention and treatment cascade. Considering multiple level interventions is imperative because they have been found to significantly increase rates of earlier testing, linkage to care and drug adherence when compared to single mode interventions. Tailored messaging, mobile clinics, and early ART initiation may be a valuable addition to primary healthcare as they reach people earlier on in their infection, decongest conventional healthcare facilities, encourage healthy behavior, and facilitate retaining clients over time.

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