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Original Article

# HIV-related stigma and universal testing and treatment for HIV prevention and care: design of an implementation science evaluation nested in the HPTN 071 (PopART) cluster-randomized trial in Zambia and South Africa

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## Abstract

**Background**: Stigma and discrimination related to HIV and key populations at high risk of HIV have the potential to impede the implementation of effective HIV prevention and treatment programmes at scale. Studies measuring the impact of stigma on these programmes are rare. We are conducting an implementation science study of HIV-related stigma in communities and health settings within a large, pragmatic cluster-randomized trial of a universal testing and treatment intervention for HIV prevention in Zambia and South Africa and will assess how stigma affects, and is affected by, implementation of this intervention.

**Methods/Design**: A mixed-method evaluation will be nested within HIV prevention trials network (HPTN) 071/PopART (Clinical Trials registration number NCT01900977), a three-arm trial comparing universal door-to-door delivery of HIV testing and referral to prevention and treatment services, accompanied by either an immediate offer of anti-retroviral treatment to people living with HIV regardless of clinical status, or an offer of treatment in-line with national guidelines, with a standard-of-care control arm. The primary outcome of HPTN 071/PopART is HIV incidence measured among a cohort of 52 500 individuals in 21 study clusters. Our evaluation will include integrated quantitative and qualitative data collection and analysis in all trial sites. We will collect quantitative data on indicators of HIV-related stigma over 3 years from large probability samples of community members, health

workers and people living with HIV. We will collect qualitative data, including in-depth interviews and observations from members of these same groups sampled purposively. In analysis, we will: (1) compare HIV-related stigma measures between study arms, (2) link data on stigma to measures of the success of implementation of the PopART intervention and (3) explore changes in the dominant drivers and manifestations of stigma in study communities and the health system.

**Discussion**: HIV-related stigma may impede the successful implementation of HIV prevention and treatment programmes. Using a novel study-design nested within a large, community randomized trial we will evaluate the extent to which HIV-related stigma affects and is affected by the implementation of a comprehensive combination HIV prevention intervention including a universal test and treatment approach.

**Key words**: Africa, AIDS, HIV, implementation science, key populations, stigma, treatment as prevention

**Key Messages**

- HIV-related stigma and discrimination can act as barriers to the implementation of successful HIV prevention programmes.
- This study is a mixed-method evaluation nested within HPTN 071/PopART, a three-arm trial comparing universal door-to-door delivery of HIV testing and referral to prevention and treatment services, accompanied by either an immediate offer of anti-retroviral treatment to people living with HIV (PLHIV) regardless of clinical status, or an offer of treatment in-line with national guidelines, with a standard-of-care control arm. The primary outcome of interest for the trial is HIV incidence.
- This study will evaluate the extent to which HIV-related stigma affects and is affected by the implementation of a comprehensive combination HIV prevention intervention including a universal test and treatment approach.

## Background

Recent advances in prevention and treatment research have led the Joint United Nations Programme on HIV/AIDS (UNAIDS 2010) to set three ambitious goals: zero new HIV infections, zero AIDS-related deaths and zero discrimination. Progress towards these aims is most critical in sub-Saharan Africa, which is the most heavily affected region in the global HIV epidemic (UNAIDS 2013). Research trials have identified partially efficacious biomedical, behavioural and structural HIV prevention interventions, including early anti-retroviral therapy for treating people living with HIV, which also has a secondary benefit of preventing HIV transmission (Hosseinipour *et al*. 2002; De Cock *et al*. 2009; Granich *et al*. 2010; Cohen *et al*. 2011; Tanser *et al*. 2013; INSIGHT Study Group 2015; TEMPRANO Study Group 2015). The challenge now is to combine these interventions and implement them at scale so that they are accessible, acceptable and adhered to by populations in need. Many of these interventions are delivered from or linked to health facilities. How stigma is manifest in health systems and communities and the potential for HIV-related stigma to undermine these interventions has been acknowledged as a persistent concern (Nyblade 2004; van Brakel 2006; Kruse *et al*. 2009; Nyblade *et al*. 2009; Watts *et al*. 2010; Stutterheim *et al*. 2014).

The 'Population Effects of Anti-Retroviral Therapy to Reduce HIV Transmission' study, known as HIV prevention trials network (HPTN) 071 (PopART), is a three-arm cluster-randomized controlled trial that will evaluate the effect of a combination HIV prevention approach that incorporates a 'universal test and treat' (UTT) strategy on community-level HIV incidence in Zambia and South Africa (Hayes *et al*. 2014). In the intervention arms A and B, the PopART intervention package includes a programme of 'universal' door-to-door delivery of HIV testing and appropriate referral and linkage to prevention and/or treatment services, including referral for prevention of mother to child transmission (PMTCT) and voluntary medical male circumcision services, depending on HIV-status. This activity is undertaken by a cadre of community-based health workers known as community HIV-care providers (CHiPs). In Arm A, clients living with HIV will be offered CHiPs-based support for linking to care and the offer of 'immediate anti-retroviral therapy (ART), regardless of CD4-count.' In Arm B, clients will be offered ART according to local guidelines. Arm C is the standard-of-care arm and will not include the CHiPs activities; however, testing and ART will be offered to all living with HIV who are diagnosed HIV-positive and accessing care through clinics, through currently available health care activities. Achieving an uptake of testing by 90% of adult household members and linkage to care (and initiation of ART in Arm A) of 80% of cases within 3 months are likely to be critical steps in the intervention reducing population-level HIV incidence (Hayes *et al*. 2014). The study includes 21 clusters (seven per arm) and the primary outcome assessment of HIV incidence will be undertaken among a population cohort of 52 500 randomly sampled adults aged 18–44 (2500 per community) over 3 years.

These hypothesized impacts will be met with many challenges. For example, delivery of ART within the HPTN 071(PopART) trial will be through existing health care facilities and experience from other studies has shown that poor adherence to another biomedical prevention technology, pre-exposure prophylaxis (PrEP) inhibited its effectiveness in two recent trials (VOICE and FEM-PrEP) in sub-Saharan Africa (Masse *et al*. 2009; Van Damme *et al*. 2012; Marrazzo *et al*. 2015). Systematic reviews suggest that stigma acts as a barrier to HIV testing (Gari *et al*. 2013; Musheke *et al*. 2013), sero-status disclosure (Smith *et al*. 2008), retention in care (Pellowski 2013) and uptake of and adherence to anti-retroviral therapy (ART) (Reisner *et al*. 2009; Katz *et al*. 2013). However, while there has been a proliferation of HIV-related stigma research,

research using rigorous designs linked to HIV interventions and drawing on implementation science approaches are largely absent (Stangl *et al.* 2013). This article describes the protocol for such a study nested within the PopART trial. The objectives are to: (1) compare HIV-related stigma measures between study arms to test whether the intervention reduces HIV-related stigma at the end of the study, (2) link data on stigma at baseline and during the trial to measures of the success of implementation of the PopART intervention to explore if and how HIV-related stigma acts as a barrier to this and (3) explore changes over time in the dominant drivers and manifestations of stigma in study communities and the health system. Three data collection points over the course of the trial allow us to measure potential changes in stigma over time using baseline and follow-up data.

## Framework and hypotheses

Erving Goffman's (1963) conceptualization of stigma as a discrediting attribute that creates a 'spoiled identity', which cuts the stigmatized person 'off from society and from himself' provides the foundation for much HIV-stigma research. Expanding Goffman's work, Link and Phelan described stigma as a harmful societal phenomenon enabled by underlying political, economic and social powers (Link and Phelan 2001). Stigma results from a four-step process beginning when a difference is marked, then linked to negative stereotypes, leading to a separation of 'us' from 'them' and finally to status loss for those who carry this marked difference (Link and Phelan 2001). Stigma can be seen as a form of social control, in which 'difference' is turned into 'inequity', as groups with power devalue and exclude other groups from society (Parker and Aggleton 2003). Although discrimination is often thought of as the end result of the stigmatization process, a range of stigma-related disadvantages can emerge such as isolation, social exclusion and reduced access to health services. Yet, in addition, stigmatization of social groups can sometimes foster activism and resilience among affected groups (Deacon 2006).

A framework we generated as part of a global effort to develop standardized indicators of HIV stigma and discrimination outlines four important concepts: drivers, facilitators, intersecting stigmas and manifestations of stigma (Stangl *et al.* 2012).

'Drivers' of HIV stigma include lack of awareness of stigma and its harmful consequences, social judgement, stereotyping and fear of HIV infection through casual contact with a person living with HIV. Although drivers are factors that negatively influence the stigmatization process, 'facilitators' can be either positive or negative. A positive facilitator is one that works to reduce stigma. For example, 'positive facilitators' include laws that protect the rights of people living with HIV, the presence of health-promotion and stigma-reduction initiatives, high levels of disclosure and openness about HIV status, accessibility of health services to all and support structures for affected groups. In contrast, 'negative facilitators' encourage stigma and may include laws that criminalize HIV transmission or same-sex behaviours or a lack of grievance redress systems for people who are discriminated against.

Drivers and facilitators influence whether individuals or groups are marked as different. Some groups may face intersecting stigmas due to HIV status, gender, profession, drug use, poverty, tuberculosis and/or sexual orientation (West 1995). The high burden of HIV in some marginalized groups has led to their further stigmatization, including within health settings. Once a person or group has been marked as different or stigmatized, a number of stigma manifestations, mostly negative, may result, including: anticipated stigma (the fear of experiencing stigma if one's HIV status becomes known or if one is marked for other reasons) (Heijnders and van der Meij 2006), perceived stigma (perceptions about how people living with HIV are treated in a given context) (Brown *et al.* 2003), internalized stigma (the acceptance among people living with HIV of negative feelings and beliefs associated with HIV about themselves) (Sengupta *et al.* 2011), shame (feeling ashamed of having a particular disease/condition) (Sengupta *et al.* 2011), experienced stigma (the experience of stigmatizing behaviours that are outside the purview of the law) (Tsai 2012; Earnshaw *et al.* 2013), discrimination (the experience of stigmatizing behaviours that fall within the purview of the law) and resilience (the power to challenge stigma) (Quinn and Chaudoir 2009). The distinction between experienced stigma and discrimination is intended solely to inform approaches for intervening to reduce the negative experiences of people living with HIV or key populations. For example, if someone is fired from their job or physically assaulted because of their HIV status, legal redress may be sought for the individual, in addition to community-level communication campaigns to improve attitudes towards people living with HIV. Drivers and facilitators of stigma are present in a range of both community (Lowther *et al.* 2014) and health care settings (Nyblade *et al.* 2009, 2013). Consequently, the presence of stigma can influence other important outcomes such as HIV care seeking behaviours, HIV testing, linkage to care, adherence to medication or quality of life.

With this backdrop, we have formulated three hypotheses that we will investigate in our research on HIV-related stigma in the context of the implementation of the HPTN 071/PopART interventions. These hypotheses are not mutually exclusive and these effects may occur simultaneously. First, the PopART intervention package may change the levels of HIV-related stigma. As suggested in the trial protocol, 'because the main intervention in HPTN 071 is universal and is offered to the entire community, it will obviate the need for specially targeted interventions for different risk groups, should help to avoid stigmatization and should encourage community-wide support for HIV prevention and care' (Hayes *et al.* 2014). If successful, the interventions may help 'normalize' HIV testing and treatment and demonstrate HIV to be preventable and treatable. The interventions may also relieve the burden on health workers and remove the need for targeted interventions, both of which may contribute to or exacerbate stigma.

A second hypothesis is that HIV-related stigma may undermine the PopART intervention's aim of translating an efficacious intervention tested from a highly controlled research settings (Cohen *et al.* 2011) to effectiveness in practice. As already outlined, stigma may pose challenges to many aspects of the PopART intervention including the acceptability of regular HIV testing, household testing, contact with lay community workers, early ART initiation and lifelong treatment adherence in entire populations (Mahajan *et al.* 2008; Pulerwitz *et al.* 2010). It is therefore plausible that the intervention may have diminished impact unless HIV and key population stigmas are more directly addressed.

A third hypothesis is that the PopART intervention may change the forms stigma takes since HIV-related stigma has proven to be dynamic, to shift in emphasis and form and manifest in subtly different ways alongside other changes. For example, because UTT makes it possible for people living with HIV to take treatment to reduce the likelihood of onward transmission, it is also possible to blame those people living with HIV who do not take treatment as acting contrary to the social good. This changes HIV-related stigma to be about social responsibility and may turn a morally pernicious gaze on people living with HIV's personal health choices. Also, assuming the

PopART intervention increases levels of testing, it is plausible that people living with HIV will become more visible as many more people learn their HIV status and start anti-retroviral therapy. This growing visibility may be accompanied by changes in stigma and/or discrimination as communities are more able to identify and label those infected, assign responsibility for transmission to people living with HIV and reinforce stereotypes. Evidence suggests that the growing accessibility of HIV treatment, and community awareness of the resource implications of this, put growing pressures on people living with HIV to 'be responsible' in taking their treatment (Kalichman 2012; Bond 2014), which may increase blame and enhance stigma manifestations for people living with HIV in areas where UTT is rolled out, thus perpetuating 'us' and 'them' distinctions which have fuelled stigma in the past.

We anticipate differences in both levels and forms of stigma between South Africa and Zambia, based on evidence from recent reports of stigma in these settings (South Africa National AIDS Council 2015). CHiPs delivering HIV care in PopART communities will receive a 9 day programme with some specific training on addressing stigma within families and stigma associated with condom use and ART adherence and will be asked to reflect on their own stigma experiences. Investigating the effectiveness of these stigma-reduction components is not a primary aim of the PopART study and there are no other specific stigma-reduction intervention components within PopART.

## Methods/design

To address these hypotheses, we will employ a multi-component study design with integrated quantitative and qualitative data collection and analysis nested within the HPTN 071 (PopART) cluster-randomized trial. The HPTN 071 trial design is described in detail elsewhere (Hayes *et al.* 2014).

### Quantitative research

Quantitative data will be collected from three different components of the trial.

#### Main HPTN 071 (PopART) trial data

First, within the main trial, a random sample of 20% of all participants in the Population Cohort aged 18–44 years of age, who are able and willing to provide informed consent, residing within the catchment area of a designated local health unit and intending to remain so for the next 3 years, and residing in a randomly selected household, will answer items on HIV-related attitudes relevant to stigma at four data collection points. The anticipated sample size at each round should be in excess of 10 000 individuals. Among the main sample, participants will also be asked to provide information about their own history of HIV testing. All participants who choose to disclose that they have previously had a positive HIV test will be asked a series of questions on their own experience of stigma and discrimination. The total sample size for this group is anticipated to be ~4000–5000 individuals.

#### Ancillary study data

Second, an ancillary study will conduct data collection complementary to, and data analysis integrated with, the main trial data. This is a mixed-methods study comprising quantitative and qualitative data collection covering all 21 PopART communities over the duration of the PopART trial (3 years). Quantitative data collection occurs in the form of an open cohort study of CHiPs (Arms A and B only) and health workers [including health facility staff and lay volunteers (Arms A–C)]. The cohort will be 'open' in that it will continue to recruit individuals who newly meet the inclusion criteria over time. Data will be collected from health care workers using electronic capture devices and will be anonymized. In the first instance, we will use cluster-level analysis strategies that link the responses of health workers and community member on HIV-related stigma to the uptake of the interventions in the study zones and communities. We anticipate recruiting over 1000 individuals to the cohort at baseline. We will formally document HIV-related attitudes, experiences of stigma and related phenomena such as job-stress among health workers and will assess how these factors influence, and are influenced by, the delivery and uptake of the HIV-related interventions that comprise PopART. Health workers are those potentially involved in the delivery or support of HIV testing and ART treatment services, or individuals with whom potential clients may interact in accessing these services. This includes doctors and nurses, as well as health facility staff who may not directly provide health services to clients, such as security guards and cleaners. A study coordinator will liaise with the community engagement office and intervention coordinator to enumerate health workers. Among this sample of health care workers, participants will also be asked to provide information about their own history of HIV testing. All participants who disclose that they have previously had a positive HIV test will be asked a series of questions on their own experience of stigma and discrimination. We anticipate the total sample size for this group to be ~100. The survey will be translated into local languages as appropriate. Efforts will be made to ensure that translations are accurate and comparable across languages through an iterative piloting process.

#### Case-control study data

Finally, three case-control studies looking at factors related to refusal and acceptance of home-based testing and re-testing, as well as initiation and non-initiation of immediate ART, will assess stigma as a potential barrier to testing and treatment.

The first case-control study will examine uptake of HIV testing during the first round of home-based testing. A random sample of 400 cases (those who refuse testing by the CHiP team) and 400 controls (those who accept testing excluding those already found to be living with HIV) will be chosen from the study communities in Arms A and B, and standardized questionnaires will be used to collect data on sexual and health seeking behaviour, previous HIV testing, as well as stigma and psychosocial questions. Cases and controls will also have sections in the questionnaire, to explore reasons for not testing and motivation to test, respectively.

In the second case-control study, carried out in Arm A only, linkage to care and initiation of ART will be examined. Cases and controls will be selected from those identified as HIV-positive by the CHiP teams and who are not already taking ART. A random sample of 400 cases (those who have not initiated ART within 6 months of being referred by CHiPs) and 400 controls (those who have initiate ART within 6 months) will be chosen from the study communities in Arm A.

The third case-control study will examine uptake of HIV testing during the second round of home-based testing in the second year of the intervention, using similar methods to those for the first case-control study.

Our approach to quantitative data collection builds on two pillars. First, we will use best-practice measures of stigma building on an indicator harmonization process we have been involved in over the past several years. Second, we will apply the idea of 'parallel'

**Table 1**. Parallel and integrative data collection modules on HIV-related stigma nested within the HPTN 071 (PopART) trial

| | Data sources/design | Sampling/sample size | Procedures |
|---|---|---|---|
| Health workers not known to be living with HIV | 1. HCW-survey:<br>Open cohort of those involved in the delivery of HIV-testing and treatment interventions. | All individuals meeting inclusion criteria, in all clusters.<br>Final recruited sample size expected to be over 1000 individuals.<br>Includes all 'CHiPs' in Arms A and B of the trial; and all Health workers linked to the health facilities in all three arms of the trial involved in the delivery or support of HIV-related services or individuals with whom potential clients may interact in accessing these services. Includes both facility-based and active community-based workers. | Survey rounds will occur in the first year of PopART delivery, after 1 year and in the final year of the study.<br>The questionnaire is comprised of eight sections. In relation to stigma, a set of 12 harmonized indicators will be asked on a 4-point Likert scale.<br>The data collection tool uses facilitated self-delivery on personal digital assistants and a local research assistant is available to answer participant questions. |
| | 2. HCW- qualitative cohort<br>A sub-group of participants in the HCW-survey (earlier). | A total sample of 40 HCWs purposively sampled to include each of the three main types of HCWs (CHiPs, facility-based and community-based health workers) and to come from different clusters, genders and age groups. | All participants in the HCW-survey are asked during the implementation of the first round of the survey whether they are willing to participate further in more in-depth qualitative exploration of their experiences. A sample of this group will be interviewed.<br>In parallel to the second round of the HCW-survey, local research assistants will consent this sub-sample and will interact with them multiple times over the subsequent 24–30 months. |
| Health workers who self-report living with HIV in HCW-survey | 3. HCW-survey (LWH)<br>Sub-group of HCW-survey who self-report living with HIV in any of the HCW-survey rounds. | All individuals meeting inclusion criteria, in all clusters.<br>Final recruited sample size expected to be 100 individuals (dependent on underlying prevalence among participants in HCW-survey and rate of self-disclosure in survey). | Per '1.' above.<br>Participants will be asked an additional set of questions about their experiences of living with HIV and delivering health services as a health care worker living with HIV. |
| | 4. HCW-qualitative cohort (LWH)<br>A sub-group of participants in the HCW-survey (earlier). | A total sample of 10 HCWs living with HIV purposively sampled to include each of the three main types of HCWs (CHiPs, facility-based and community-based health workers) and to come from different clusters, genders and age groups. | Per '2.' above.<br>Participants will also be asked to explore their HIV 'illness' narrative and their experiences accessing care as a patient. |
| People living in the catchment areas of the intervention clinics not known to be living with HIV and/or not a member of a key population group | 5. Longitudinal ethnography of families living in intervention communities | A total sample of ~40 families purposively sampled to include families from each arm of the study. | Families are identified for follow-up from a longer list of potential families recruited through purposive, door-to-door sampling informed by prior formative research in each cluster.<br>Data are collected ethnographically, including multiple home contacts for discussions and *in situ* observations over the course of 36 months. |
| | 6. Sub-sample of population cohort (end-point evaluation cohort for HPTN 071 trial) | Simple random sample of enumerated houses. All adult residents aged 18–44 years listed, and one age-eligible resident selected at random who is invited to join the population cohort. A random 20% of all participants at each round will answer questions on HIV-related attitudes relevant to stigma.<br>Final sample size for stigma-related questions will likely be over 10 000 individuals at each survey. | Questionnaire is undertaken and blood sample is collected and stored for retrospective testing which will include HIV testing and other secondary outcome measures.<br>All cohort members, irrespective of HIV status, will be followed after 1 and 2 years (interim surveys) and 3 years (final survey) to measure HIV incidence and other factors including stigma. |

continued

**Table 1.** Continued

| | Data sources/design | Sampling/sample size | Procedures |
|---|---|---|---|
| | 7. Case-control 1: cross-sectional survey of HIV test non-acceptors vs acceptors<br>And<br>Case-control 3: cross-sectional survey of repeat HIV test accepters vs decliners | Four hundred non-acceptors (cases) and 400 acceptors (controls) of home-based HIV testing by CHiPs, during the first and second years of the intervention.<br>Cases and controls from the communities in Arms A and B will be enrolled. Potential participants will be selected at random and approached by CHiP personnel, who will seek verbal consent for follow-up by a research team. The latter will then obtain the formal informed consent for case-control study participation. | Interviews will be carried out by case-control study teams using standardized questionnaires after the end of the first and second CHiP home-based testing round within a community and will encompass questions about a range of characteristics, opinions and behaviours including sexual and health seeking behaviour, previous HIV testing, as well as stigma and psychosocial questions. Cases and controls will also have separate sections in the questionnaire, to explore reasons for not testing and motivation to test, respectively. In the second year, there will also be sub-group analyses to consider participants who: (1) accepted, tested and were found negative at the first round, (2) refused testing at the first round and (3) were absent at the baseline testing round (away from home or newly moved into community). |
| People living in the catchment areas of the intervention clinics | 8. Longitudinal ethnography of families affected by HIV living in intervention communities | A total sample of ~20 families purposively sampled to include families from across each arm of the study. The sample will also purposively including people living with HIV who are early initiators on ART, initiators per national guidelines and not (yet) on ART.<br>Each family will include at least one person who discloses this to the research team (and not necessarily to other member of their family) over the course of the data collection period. | Families are identified for follow-up from a longer list of potential families recruited through purposive, door-to-door sampling informed by prior formative research in each of the study clusters, and from participants in case-control Studies 1 and 2.<br>Data are collected per '5.' above.<br>Individual interviews with the person(s) living with HIV in each family will be conducted to facilitate these participants' description of their illness narratives. |
| | 9. Sub-sample of population cohort (end-point evaluation cohort for HPTN 071 trial) who self-report living with HIV | All individuals in the population cohort and health worker survey who self-identify as having previously having had an HIV test that was HIV-positive will be asked a specific set of additional questions focusing on such aspects as treatment access and experiences of stigma and discrimination.<br>HIV prevalence is expected to be 15%. We anticipate over 4000 community members and 100 health workers living with HIV to be interviewed at each round.<br>As for the population cohort and health workers studies, except this component will include only respondents who additionally report are living with HIV. | Stigma-related questions among this group include 12 items that assess shame, internalized stigma, experienced stigma, experienced discrimination and resilience.<br>Health workers living with HIV participating in the health care worker survey receive an additional four questions to assess stigma they may have anticipated or experienced as a health care worker living with HIV (Table 2). |
| | 10. Case-control 2: cross-sectional survey of CHiP clients living with HIV who link to ART within 6 months of referral vs non-linkers | Four hundred people who do not initiate 'immediate*' ART (cases) and 400 people who initiate 'immediate*' ART (controls), in Arm A during the first year of the intervention.<br>Cases and controls from the communities in Arm A will be enrolled. Potential participants will be selected at random and approached by CHiP personnel, who will seek verbal consent for follow-up by a research team. The latter will | Standardized questionnaires will encompass sexual and health seeking behaviour, as well as stigma and psychosocial questions. Data collection procedures as per '7' above. |

continued

**Table 1.** Continued

| | Data sources/design | Sampling/sample size | Procedures |
|---|---|---|---|
| | | then obtain the formal informed consent for case-control Study 2 participation. | |
| People living in the catchment areas of the intervention clinics who are members of key population groups | 11. Longitudinal ethnography of families living in intervention communities in which one or more family member is part of a key population group | A total sample of ~20 families purposively sampled to include families with members who are also members of different key population groups.<br>The total sample size will be informed by ongoing data collection, including preliminary analysis of baseline data from the HCW-survey. The researchers will adapt the sampling to focus on those key populations most important to understanding stigma in the context of UTT. | Families are identified in collaboration with local stakeholders providing services to members of the key population groups through a stakeholder mapping exercise conducted in each cluster.<br>Data are collected per '5.' above.<br>As per '8' above, individual interviews with the person(s) who are also a member of key population group in each family will be conducted. |

assessment of stigma in interactions between individuals from different groups to address the same phenomena from multiple perspectives. We describe these aspects in more detail later.

Diversity in the measures used to assess HIV-related stigma has been a growing barrier to synthesis and quality appraisal of the evidence base (Mahajan *et al.* 2008; Katz *et al.* 2013; Stangl *et al.* 2013). A large number of measures have been used in a variety of cultural contexts and with various populations. From 2010 to 2014, a consultative process supported by UNAIDS reviewed existing measures, identified key stigma domains and developed measures that would aid synthesis across studies among the general population, health care workers and people living with HIV. Through consultation, eight measures were recommended, field-tested in the Rwanda 2011 DHS and subsequently reviewed and approved by the UNAIDS' monitoring and evaluation reference group (MERG) in 2014 (Nyblade *et al.* 2013). Related measures for health care workers were also developed and approved by the MERG in 2014 (Nyblade *et al.* 2013). We adopted these measures as a starting point for our work, with only minor changes necessitated by context. For example, we used 4-point Likert response categories in our questionnaires, assessing strength of agreement with statements, as opposed to dichotomous (yes/no) response categories, which necessitated slight phrasing changes. The Likert items will allow us to capture degrees of feeling and obtain more accurate responses. The specific drivers and manifestations of stigma being asked about remained the same.

The idea of parallel assessment of HIV-related stigma, i.e. assessing the same stigma criteria among clients in the general population receiving the PopART intervention, health care workers in the stigma ancillary study and participants in the case-control studies, is to address the same phenomena from multiple perspectives (Visser *et al.* 2008). For example, community members can report on their perception of discriminatory acts towards people living with HIV; people living with HIV, including health care workers, can report on the actual experience of stigmatization; while health workers can report on their perceptions of their and their co-workers' treatment of people living with HIV, which may be stigmatizing. Assessing stigma from these multiple perspectives will be a cornerstone of our approach. Although the use of parallel measures has been previously recommended for studying HIV-related stigma (Stangl *et al.* 2012; Nyblade *et al.* 2013), our study provides the first opportunity to implement parallel measurements across multiple groups on a large scale. A detailed description of these parallel measures is provided in Table 1.

Building on these principles, Table 2 provides details of how we will use agreed wording in relation to core stigma phenomena to assess these phenomena from multiple perspectives. We used key wording from the harmonization process as the starting point. As we have already described, stigma starts with separation between 'us' and 'them'. This separation in turn leads to a variety of ways in which the dominant 'us' may relate to 'them'. The manifestations of stigma towards 'them' by the dominant group include: *fear, consider irresponsible, lose respect for, not want to sit next to, talk badly about, verbally insult* or *physically assault*. These wordings cover a range of aspects of the stigmatization process as it has been shown to unfold in a range of settings. Our study is concerned with a range of 'us' and 'them' interactions. The potentially dominant 'us' groups include the community at large and health workers. Groups at risk of HIV-related stigma ('them') include *people known or thought to be living with HIV*, but also *young women who get pregnant before marriage, men who have sex with men, female sex workers, migrants (including migrants from other parts of Africa, non-African international migrants, nationals from other parts of the country*

**Table 2.** Parallel stigma measures collected across study populations for HPTN 071 (PopART) stigma ancillary study

| Stigma construct | Who reports | What perspective do they report on? |
|---|---|---|
| Drivers | | |
| Fear | Community members | I **fear** that I could contract HIV if I come into contact with the saliva of a person living with HIV |
| | Health workers | I **fear** that I could contract HIV when providing services to. . .[a] |
| Stereotype | Community members | People get HIV because they **engage in irresponsible behaviours** |
| | Health Workers | . . .[a] **engage in irresponsible behaviours** |
| Manifestation | | |
| Anticipated stigma | Community members | People are hesitant to take an HIV test due to **fear of other people's reaction** if the test result is positive for HIV |
| | Health workers | |
| | Testers/Non-Testers | |
| Shame | Community members | I would be **ashamed** if someone in my family had HIV |
| | People living with HIV (PLHIV) (including initiators and non-initiators of immediate ART) | I have felt **ashamed** because of my HIV status |
| | Health Workers | I would be **ashamed** if someone in my family. . .[b] |
| | Testers/Non-testers | People are **ashamed** if the test result is positive for HIV |
| | Testers/Non-testers | I would be **ashamed** if someone in my family had an HIV test |
| Status loss | Community members | People living with or thought to be living with HIV **lose respect and standing** |
| | PLHIV | I have **lost respect or standing** in the community because of my HIV status |
| | Health workers | . . .[a] **lose respect or standing** |
| Verbal abuse | Community members | People sometimes **talk badly about**. . .[a] |
| | PLHIV (including initiators and non-initiators of immediate ART) | |
| | PLHIV | People have **talked badly about** me because of my HIV status |
| | Community members | Health workers sometimes **talk badly about** people living with or thought to be living with HIV to others |
| | PLHIV | Health workers **talked badly about** me because of my HIV status |
| | Health workers | My co-workers sometimes **talk badly about**. . .[c] |
| | Community members | People living with or thought to be living with HIV are sometimes **verbally insulted, harassed and/or threatened** |
| | PLHIV (including initiators and non-initiators of immediate ART) | |
| | PLHIV | I have been **verbally insulted, harassed and/or threatened** because of my HIV status |
| | Health workers | My co-workers sometimes **verbally insult** clients living with HIV |
| Physical abuse | Community members | People living with or thought to be living with HIV are sometimes **physically assaulted** |
| | PLHIV | I have been **physically assaulted** because of my HIV status |
| | Health workers | . . .[c]are sometimes **physically assaulted** |
| Unwanted disclosure | Community members | People sometimes **disclose** that other people are HIV-positive without their permission |
| | PLHIV (including initiators and non-initiators of immediate ART) | Someone else **disclosed** my HIV status without my permission/people have disclosed my HIV status to others without my permission |
| | Community members | Health workers sometimes **disclose** that other people are HIV-positive without their permission |
| | PLHIV (including initiators and non-initiators of immediate ART) | A health worker **disclosed** my HIV status without my permission/a health worker may disclose to others without my permission that I am on treatment for HIV (if I am on treatment) |
| | Health workers | My co-workers sometimes **gossip** about clients HIV test results |
| Internalized stigma | PLHIV (including initiators and non-initiators of immediate ART) | I have lost respect or standing because of my HIV status |
| | | I think less of myself because of my HIV status |
| | | I have felt ashamed because of my HIV status |

[a]question includes variations with the following populations: people thought to be living with HIV, young women who become pregnant before marriage, female sex workers or men who are thought to have sex with men.

[b]question includes variations with the following: became pregnant before marriage, sold sex, had sex with other men or had a disability.

[c]question includes variations with the following populations: young women who become pregnant before marriage, female sex workers, men who are thought to have sex with men, people with disabilities and migrants.

The entries in bold represent the manifestations of stigma that we refer to in the study. These are the statements that are parallel across questions about multiple populations.

*and transient people who move between places and do not have a set address in study communities)* and *people living with disability*. In addition, we hypothesize that those *who accept HIV testing* and *initiate anti-retroviral treatment*, may potentially be stigmatized or that there may be anticipation of this by those considering accessing these services. We note that individuals can occupy both 'us' and 'them' roles in different aspects of their lives (e.g. a person may be both a health worker providing HIV-related services, and themselves a person living with HIV), as well as occupy intersecting membership of potentially stigmatized groups (such as in the case of a female sex worker who is also HIV-positive).

With this framework in place, we will ask questions about 'us'/'them' interactions in the study settings over the course of the study from a range of perspectives (Table 2). For example, stigmatized individuals being '*talked badly about*' is a key manifestation of stigma. We will ask about this phenomenon from a range of perspectives. Community members will be asked to respond to the extent to which they agree that people living with HIV are talked badly about; people living with HIV will be asked how often this has happened to them; and health workers will be asked their strength of agreement that their co-workers talk badly about people living with HIV or people from the various other potentially stigmatized groups described earlier. Table 2 provides a range of other examples of this parallel wording approach.

## Integrated qualitative research

Comprehensive research on health-related stigma requires qualitative methods to be applied (Scambler *et al.* 2006). Qualitative research has been integrated into the survey processes and will also be conducted independent of the surveys. Our qualitative approaches will be flexible and iterative over the course of the trial to respond to emergent understandings of stigma (including baseline analysis of the quantitative data). We describe here four ways in which qualitative data will contribute to the study objectives and provide details about data collection in the design and early stages of the work.

First, the survey tools were developed partly by drawing on ethnographic and qualitative findings on local context, the dynamics of HIV-related stigma and the specific health facilities and service delivery in both countries (Bond *et al.* 2013). Further, during the survey implementation, we will undertake regular formal debriefing of staff to iteratively document and explore both participants' understanding of the survey and other influences on the uptake of the survey. This includes collecting and analysing comments from participants and systematic researcher reflections on the actual conduct of the survey in each health facility (Mathema *et al.* 2015). Emerging findings from analyses of quantitative data may inform qualitative research processes while the qualitative data can also be used to attach more meaning to quantitative outcomes.

Second, we will use qualitative methods to investigate interactions between health workers, community members, people seeking or being offered HIV-related services and people living with HIV. In accordance with our focus on how stigma influences the implementation, and thus success, of HPTN 071 (PopART), we will recruit ~40 selected health workers (15 CHiPs, 15 health facility staff and 10 supervisors or managers of both groups) with whom we will interact on an individual basis each year during PopART implementation. We will undertake semi-structured interviews on their life histories, reflections on their work activities and their experience of stigma (in the health system, in ART delivery and other HIV services). The health workers will be purposively sampled for diversity (in age, gender, time working as a health worker, cultural group, trial Arm and site community type). In addition to the interviews, qualitative data will be collected via structured observations of health service delivery in each of the 21 health facilities. These observations will be conducted close to the survey implementation periods to understand manifestations of stigma in health care workers' working environment. Across the PopART study communities, we will also undertake rapid community appraisal, ethnographic research, media reviews and participant observation at intervals during the intervention period as well as in response to any events (including policy and programmatic changes) as part of a broader social science agenda. This research is carried out by social science researchers and research assistants. The methods (supported by accompanying tools) used will include conducting transect walks and observations of places of relevance, accompanying key intervention and research personnel in the field, observing clinic practice and community mobilization, attending stakeholder meetings, longitudinal interviews and on the spot interviews with key individuals and households, group discussions with different age and gender groups and systematic review of relevant media. All audio recordings of data will be transcribed and translated verbatim. These research methods will capture the perspectives of community members and people living with HIV across a range of settings and contexts (Yin 2009; Butler-Kisber 2010). Stigma will be one of the key themes embedded in the coding structure applied to these data as they emerge.

Third, our research seeks also to understand the particular challenges faced by some population groups in accessing HIV-related services. In the first year, a series of exploratory life history/illness narrative interviews will be undertaken with a small number of representatives from a diversity of populations (including, but not limited to, groups such as female sex workers and men who have sex with men) as a context-specific situational analysis. These interviews will be used to tailor further data collection processes with other members of each key population group to be implemented (as necessary) from year two onwards. Informants will be selected on the basis of 'critical-case sampling', a form of purposive sampling where participants are recruited on the basis of prior expectation that they are knowledgeable or have much experience of the phenomena or topic being studied. These interviews will take place over four study visits, spread over 3–4 weeks and may form the basis for iterative, multi-method research in subsequent years among those assessed to be highest priority for understanding the importance of HIV-related stigma in the delivery of the PopART intervention (specifically) and UTT (in general).

Finally, we will document how changes in HIV services (e.g. PMTCT Option B+ and other changes in treatment guidelines) and efforts to reduce HIV-related stigma, and events that may undermine these efforts, unfold over the course of the study. A rapid stakeholder survey in the first intervention year will capture definitions and targeted interventions for key population groups and stigma-reduction activities and materials. This will be updated annually and related to events. Regular structured documentation and observation of public, study specific and relevant emerging events, health facilities and stigma-reduction activities as well as routine debriefing of field staff will be carried out. Study documentation, media articles and other documentation relevant to the aims of this study will be collected by the research team at national and community site level. These data will provide parallel and more holistic findings on the relationship between HIV-related stigma and the delivery of HIV services at this stage of the HIV epidemic response and ART roll-out in both countries.

Our innovative framework for parallel, mixed-method data collection on HIV-related stigma using harmonized indicators in the context of a cluster-randomized trial will give rise to a rich data set.

The first step in the quantitative analysis will be the development of locally relevant scales to measure different domains of the stigmatization process. As described earlier, we have mapped specific items in our questionnaires to different domains of HIV-related stigma (Table 2). Following baseline data collection, we will finalize scale development approaches, informed by qualitative research and following descriptive analysis of the data. Associations between items will be explored and appropriate data reduction techniques will be used to group information from different items but related to common underlying concepts. For some of our aims, we will develop a single community-level measure of the severity of HIV-related stigma. Following the baseline analysis, all scales for use in follow-up assessments will be specified in an analysis plan published/archived in advance of end-line analyses.

Table 1 summarizes the study methods with population groups from whom we will collect data.

**Analytical procedures**

Our treatment of the stigma measures within analysis will depend on the specific research question at hand. The analytic approaches that will be used to address our three primary hypotheses are described later. It should be noted that qualitative analysis will be carried out using two approaches in relation to the key hypotheses. In response to quantitative analysis outcomes when appropriate (e.g. to extend our understanding of a strong outcome or to explore what underlies an anomaly), qualitative understanding will be sought either through new enquiry or through existing qualitative data. And, more independent of quantitative analysis, qualitative analysis will be conducted around key population groups and key areas of interest and relevance. Some of these areas will be covered also by the quantitative data—but others will be areas that are more appropriately researched through qualitative methodology. The latter includes differences across site communities (and health facilities) and countries, attitudes to key population groups and shifts in specific forms of stigma over time and in response to changes in treatment guidelines and delivery and other HIV services. Although both quantitative and qualitative approaches will be integrated in relation to all three hypotheses, we provide more detailed description of the use of quantitative data from Hypotheses 1 and 2 and qualitative data for Hypothesis 3 later.

*Hypothesis 1: does PopART reduce HIV-related stigma?*. HIV-related stigma is a pre-specified secondary outcome for the trial. To address this hypothesis, we will compare stigma measures across the randomized trial arms over time, using the analytical methods for the primary analysis of trial outcomes for the main trial. The primary comparison will be between study arms at follow-up; a secondary analysis will look at trends over time (before and after comparisons) in each arm. In brief, the approach is based on a comparison of cluster summaries using Student's t-test, which has been shown to be highly robust for small numbers of clusters. We will compute cluster summaries of HIV-related stigma measures based on the scale development approaches described earlier. To test the null hypothesis of no impact, the paired t-test will be applied to pairwise cluster comparisons of these summary measures (Arm A vs Arm B, Arm A vs Arm C, Arm B vs Arm C—seven matched pairs for each comparison), with 6° of freedom. Evidence for intervention effect will also be assessed using a non-parametric permutation test approach described in the main protocol. We will adjust analyses for baseline imbalances where appropriate using a two-stage approach (Hayes and Bennett 1999).

*Hypothesis 2: does HIV-related stigma act as a barrier to the implementation and effectiveness of PopART?*. Addressing this hypothesis will require an analysis strategy that does not directly compare clusters randomized with the different study arms. Instead, we will exploit naturally occurring variation in levels of HIV-related stigma among health workers and communities and explore whether this variation is associated with uptake of and adherence to the PopART interventions in study clusters after adjusting for potentially confounding factors. Indicators of HIV-related stigma will be treated as exposure variables. The 'outcome' variables will be measures of the uptake of key components of the PopART intervention package over years 1–3, requiring outcome data drawn from the population cohort (i.e. HIV testing, linkage to care, initiation of ART and adherence to ART) and other data sources. The operationalization of these variables will be finalized in-line with plans for the main trial analysis since several of these variables are specified as secondary outcomes. In the first instance, we will use cluster-level analysis strategies that link the responses of health workers, including CHiPs and health facility staff, on HIV-related stigma to the uptake of the interventions they offer in the zones and clusters in which they work. It will be necessary to adjust for potential confounding factors that may also influence the uptake of PopART interventions, including trial arm, country and sociodemographic factors among both CHiPs/HFS and the target populations. For further analyses, after completion of intervention delivery for the trial and subject to ethics approval, we plan to analyse associations at individual level between stigma measures from the health worker surveys and uptake of PopART services delivered by these health workers, based on anonymized linkage of data. Data will be presented at the triplet and arm level separately and clinic names will not be used. Data will be aggregated over communities and only presented at the level of study arm or match triplet. This will ensure that data remain anonymous.

*Hypothesis 3: do the dominant forms and manifestations of stigma and discrimination shift as the interventions roll-out?*. Our primary approach to document changes in the forms of stigma in study communities will be through analysis of the qualitative data. This hypothesis is by definition exploratory, as we cannot yet know how forms and manifestations of stigma and discrimination might shift. Particular analyses will be defined in response to observed changes following analytic goals determined by iterative engagement with the research communities. Explanations for observations will be proposed using inductive logic, with content, thematic and discourse analytic methods used, as appropriate, to refine these explanations. All audio recordings of qualitative data will be transcribed and translated to English verbatim. All transcripts, field notes, structured observation activities and any other form of qualitative data are managed in ATLAS.ti (v7). Initial coding of the data will be deductive and follow the hypotheses outlined earlier, with subsequent finer analyses following inductive coding.

## Trial status

As of 1 December 2014, HPTN 071 (Division of AIDS [DAIDS] #11865 and Clinical Trials registration number NCT01900977) received institutional review board (IRB) approval from the London

School of Hygiene and Tropical Medicine (LSHTM), the Desmond Tutu Tuberculosis Centre (DTTC) and the University of Zambia. The trial is being implemented in Zambia and South Africa. The stigma ancillary study (DAIDS # HPTN 071a) has received IRB approval from LSHTM (February 2014) DTTC (February 2014), University of Zambia (October 2014) and the International Centre for Research on Women (ICRW) (January 2014). The stigma ancillary study received site activation from DAIDS in both countries (South Africa, July 2014; Zambia, October 2014). Written informed consent will be sought and obtained from all participants in all aspects of the research. All participants (including the survey participants and participants who consent to any aspect of the qualitative research) will have their confidentiality protected, including from other members of the HPTN 071 study management structures. All presentations of data will be anonymized with appropriate use of pseudonyms and other mechanisms for participant identity when reporting qualitative findings. In addition, the identity of communities, clinics and other service teams will be similarly protected.

## Discussion

In addition to reducing numbers of HIV infections and deaths from AIDS-related causes, accelerating reductions in HIV-related stigma in sub-Saharan Africa is a key policy objective (UNAIDS 2010). The continued roll-out of effective HIV prevention and treatment interventions may contribute to stigma reduction (Granich *et al.* 2009). Conversely, HIV-related stigma may act as a powerful barrier to translating the efficacy of these interventions in research trials to effectiveness in practice (Katz *et al.* 2013, 2015). Forms of HIV-related stigma may shift as the response changes over time. These hypotheses have rarely been formally addressed in research trials or with implementation science research methods. We have outlined a data collection and analysis protocol addressing these questions, nested within the context of a large cluster-randomized trial of a UTT strategy for HIV prevention in Zambia and South Africa.

Our study has many strengths. We will implement many best-practice aspects of stigma-related research recommended in the literature but rarely practiced. We will collect data on stigma in a parallel fashion (Stangl *et al.* 2012), questioning research participants from different stakeholder groups using items and tools that address the same underlying phenomena. The timing of our study comes following a recent harmonization process designed to improve quality and reduce the heterogeneity with which HIV-related stigma is measured in research studies, and we will deploy these approaches in our research (Stangl *et al.* 2012; Nyblade *et al.* 2013). We have large sample sizes to address our quantitative research questions and an integrated programme of qualitative research running alongside the quantitative work. Finally, the study is nested within a cluster-randomized trial allowing us the benefits of this research design in addressing some of our key hypotheses.

There are also potential challenges. One potential threat to the study is if our measurement of HIV-related stigma is biased or does not capture key aspects of relevance to our hypotheses. It is possible that people who decline to take part in the stigma study may be those who are most uncomfortable talking about and admitting to stigma. As described earlier, our tools are driven by best-practice approaches and experience, reducing the chance of missing important domains of stigma. However, space within questionnaires is limited, and inevitably compromises will need to be made. Further, conducting research on sensitive subjects such as attitudes to HIV-related stigma is complex (Earnshaw *et al.* 2009). This complexity is heightened in our study by the focus in one aspect of our research on data collection with health workers, some of whom are employed, for the duration of the trial, by the same organization as the research team. This poses both ethical and potential data validity challenges, and we have considered a number of approaches to minimize these challenges. Research procedures are designed to maximally demonstrate to participants that their participation is entirely voluntary, that their responses are fully confidential, including from any members of staff involved in management of intervention components, and that there are no right or wrong answers to the questions we pose. In this way, we hope to off-set potential vulnerabilities described in the literature where research is conducted with employees (Kipnis 2001; Horn 2007) and to maximize data validity. It will be essential for us to maintain a high-level of vigilance as our fieldwork progresses in relation to these matters.

These limitations notwithstanding, we anticipate that the outputs of our research will have important implications for policy and future research agendas. This is perhaps best captured by considering two extreme scenarios. If the PopART intervention is both successful in reducing HIV infections and in reducing levels of HIV-related stigma, this may suggest that major, stand-alone HIV stigma-reduction initiatives beyond those already in place will not be necessary to make progress. It may also suggest less need for targeted interventions in settings where universal access to testing and treatment is to be implemented. Stigma reduction is an inherent component of several HIV prevention interventions. For example, information and education campaigns in schools, health settings and workplaces address the aim of reducing stigma, both indirectly by providing up-to-date accurate information and, in some cases, by addressing stigma more directly. The training for new health workers recruited to deliver the PopART intervention includes a brief component addressing ways to avoid stigmatization in working practice. Although the presence of these interventions may be important, our study may suggest that a greater focus on stigma reduction and targeted interventions for stigmatized groups is not necessary to reduce stigma if PopART-style interventions are successfully rolled out more widely.

An alternative extreme scenario is that the PopART intervention may be unsuccessful in achieving its aims of reducing HIV incidence. Although HIV-related stigma is one critical factor that might impede the success of the PopART intervention, it is not the only one and may not work in isolation. Overburdened health systems may also struggle to deliver the strategy without significant additional resources. The extent of behavioural risk disinhibition (Bunnell *et al.* 2006), levels of anti-retroviral toxicity, the availability of second and third line treatment regimens and the number of transmission events that occur during acute HIV infection (Brenner *et al.* 2007; Hollingsworth *et al.* 2008; Pinkerton 2008) will also be critical determinants of the success of a UTT intervention and may themselves be linked to stigma. We will need to place stigma within this range of potential explanations. Nevertheless, data from this study may support the conclusion that HIV-related stigma in communities and health settings was an important contributor. In such a scenario, our recommendations will focus on two things. First, they will emphasize the potential importance of a more rigorous and intensive focus on stigma reduction to accompany the roll-out of combination HIV prevention approaches. Second, our research will provide valuable information on appropriate content and delivery mechanisms for such supporting interventions. These findings would give greater urgency and importance to the ongoing and future conduct of rigorous research trials of interventions designed to address HIV-related stigma.

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