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Reducing intersectional stigma among transgender women in Brazil to promote uptake of HIV testing and PrEP: study protocol for a randomised controlled trial of Manas por Manas

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ABSTRACT

Introduction Globally, transgender ('trans') women experience extreme social and economic marginalisation due to intersectional stigma, defined as the confluence of stigma that results from the intersection of social identities and positions among those who are oppressed multiple times. Among trans women, gender-based stigma intersects with social positions such as engagement in sex work and substance use, as well as race-based stigma to generate a social context of vulnerability and increased risk of HIV acquisition. In Brazil, trans women are the 'most at-risk' group for HIV, with 55 times higher estimated odds of HIV infection than the general population; further, uptake of HIV testing and pre-exposure prophylaxis (PrEP) among trans women is significantly lower than other at-risk groups. Through extensive formative work, we developed Manas por Manas, a multilevel intervention using HIV prevention strategies with demonstrated feasibility and acceptability by trans women in Brazil, to address intersectional stigma and increase engagement in the HIV prevention continuum.

Methods and analysis We are conducting a two-arm randomised wait-list controlled trial of the intervention's efficacy in São Paulo, Brazil, to improve uptake of HIV testing and PrEP among transgender women (N=400). The primary outcomes are changes in HIV testing (self-testing and clinic based), changes in PrEP uptake and changes in PrEP persistence at baseline and follow-up assessment for 12 months at 3-month intervals.

Ethics and dissemination This study was approved by University of California, San Francisco Institutional Review Board (15-17910) and Comissão Nacional de Ética em Pesquisa (Research Ethics National Commission, CAAE: 25215219.8.0000.5479) in Brazil. Participants provided informed consent before enrolment. We are committed to collaboration with National Institutes of Health officials, other researchers, and health and social services communities for rapid dissemination of data and sharing of materials. The results will be published in peer-reviewed academic journals and scientific presentations.

Trial registration number NCT03081559.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ 'Manas por Manas' is a theory-based, peer-facilitated, multilevel stigma reduction intervention informed by decades of research by a multidisciplinary team in Brazil and the USA.
⇒ This randomised controlled trial (RCT) was implemented in an urban setting with large numbers of transgender women, in a context where pre-exposure prophylaxis and HIV self-testing are available publicly, providing an opportunity to evaluate and scale up an HIV prevention initiative in a key health disparities population.
⇒ This RCT contributes to nascent research in intersectional stigma.
⇒ A limitation of the intervention approach is that many challenges contribute to HIV-related disparities among transgender women in Brazil, including social, economic and structural factors.
⇒ The COVID-19 pandemic forced the study to pivot to virtual group and individual peer navigation sessions early in the research. Health services for some participants were limited, and social distancing requirements likely impacted sexual relationships and thus HIV prevention needs.

INTRODUCTION

Background and rationale

Transgender ('trans') women in Brazil experience multiple stigmas that complicate their access to and adherence to healthcare, resulting in intersectional stigma and negative health outcomes. Stigma is a social process enacted through social structures and interpersonal interactions that devalues human difference, marginalises stigmatised individuals and creates a social hierarchy that reinforces social inequality.[1] Stigma is a fundamental cause of health disparities.[2] Intersectionality is a theoretical approach

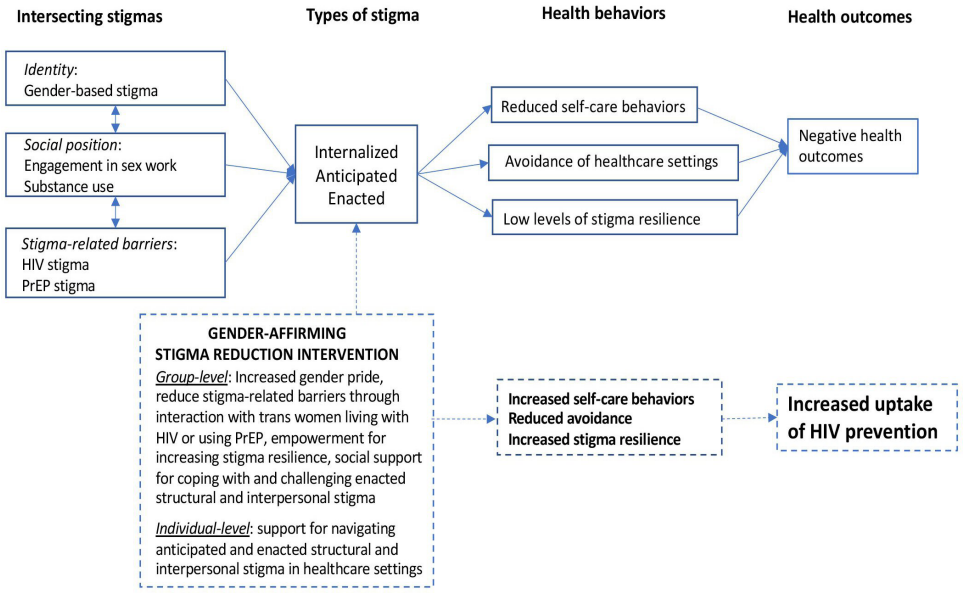

Figure 1 Conceptual framework for intersectional stigma reduction intervention

that highlights how multiple types of oppression intersect to create and reinforce social inequalities.[3] Thus, intersectional stigma is defined here as *the confluence of multiple stigmatised identities, social positions and stigma-related barriers that result in structural inequalities and health disparities.*[3] Due to gender-based stigma, trans women face extreme social and economic marginalisation that lead to additional stigmas based on social positions, such as engagement in sex work and substance use,[4 5] which also intersect with race-based stigma. Further, these identity-based and social position-based stigmas intersect with stigma-related barriers such as pre-exposure prophylaxis (PrEP) stigma[6] and HIV stigma[7] to drive low rates of HIV testing, PrEP uptake and PrEP persistence among trans women. Experiences of *enacted stigma* (experiences of being stigmatised and/or discriminated against) often lead trans women to *anticipate stigma* (expectations of experiencing stigma) from healthcare providers, which in turn leads to healthcare avoidance and the internalisation of stigma[8] (adopting stigmatising attitudes toward oneself; see figure 1 for conceptual framework). *Stigma resilience* is the ability to cope with and/or challenge enacted stigma, seek healthcare despite anticipated stigma and resist internalisation of stigmatising beliefs,[9–11] which includes being empowered in one's healthcare[12] despite the context of stigma.

Largely driven by stigma, trans women have some of the highest rates of HIV in the world and are at the highest risk of HIV in Brazil. A recent meta-analysis of pooled data among trans women from 10 low-income countries found 50 times increased odds of HIV compared with other adults and an HIV prevalence of 18%.[13] In South America, HIV prevalence estimates as high as 30% have been documented in population-based studies among trans women.[14] In Rio de Janeiro, 31% of trans women recruited through respondent-driven sampling were living with HIV, 7% were new diagnoses; almost one-third (29%) of their participants had not been previously tested.[15] Additional data corroborate that trans women are the 'most at-risk' group in Brazil,[16] with estimated odds of HIV diagnosis among trans women over 55 times higher than the general Brazilian population,[17] placing Brazil among countries with the greatest HIV disparities.[13]

Despite high rates of HIV, HIV testing and uptake of PrEP among trans women are significantly lower than other groups. Trans women report activities that increase risk of HIV exposure, including condomless anal sex with multiple partners,[18 19] high number of sex partners,[20] sex while using drugs and alcohol,[21] and sex work,[22 23] yet they frequently underestimate their risk of acquiring HIV[18] and have low rates of HIV testing.[24] Oral PrEP has been shown to reduce risk of acquiring HIV by 92% among adherent users.[25] However, one study of PrEP uptake and adherence among trans women found that although they had high uptake (48%) and retention (85.4%) in the study, adherence was relatively low—only 48.6% had high PrEP adherence.[26] In Brazil, awareness of PrEP is low among trans women despite its free availability through the Brazilian universal health system or Sistema Único de Saúde (SUS).[27] One study in Rio de Janeiro found that among 345 participants offered HIV testing, 204 (59.1%) were not living with HIV, 101 (29.3%) had previously been diagnosed with HIV and 40 (11.6%) were newly diagnosed with HIV. Of those who were not living with HIV, 131 (38.0%) had heard of PrEP at the time of the survey, 76% were willing to use PrEP once they were aware of it and 67% met PrEP behavioural eligibility criteria.[28] Despite eligibility and willingness to use PrEP, as of August 2018, only 74 Brazilian trans women had initiated PrEP through SUS nationally.[29] The São Paulo state PrEP monitoring report notes a need for new strategies to promote PrEP uptake among trans people.[30]

Multilevel interventions that address intersectional stigma to increase uptake of HIV testing and PrEP are

urgently needed to improve health outcomes among trans women in Brazil. Working at both the group and individual levels, we have developed Manas por Manas, a trans-specific, gender-affirming group empowerment and peer navigation intervention to address intersectional stigma, thereby improving the HIV prevention continuum, namely HIV testing and PrEP uptake, among trans women in Brazil. While structural interventions are crucial for long-term social change, it is also critical to increase stigma resilience among trans women through support and empowerment that are urgently necessary to navigate existing systems that cannot be immediately reformed and where stigma is pervasively enacted against transgender people[31 32] and continues to fuel HIV transmission.[33] To have an immediate impact on the lives of trans women, we must work to increase stigma resilience to support trans women in navigating current systems of care.[1 34]

This study is a randomised wait-list controlled trial testing Manas por Manas, designed to address intersectional stigma among transgender women in São Paulo, Brazil. Manas por Manas is comprised of two intervention components: (1) a group-level, peer-led intervention and (2) an individual-level peer navigation programme to increase uptake of HIV testing and PrEP. Manas por Manas is informed by our team's trans-specific conceptual model, Gender Affirmation,[35] that describes intersectional stigma faced by trans women, informs investigations of how intersectional stigma results in health disparities, and provides a framework for intervention development and testing.

Choice of comparators

We selected a wait-list control condition, in which participants randomised to the control condition are offered the intervention content after their final assessment point, to safeguard ethical treatment of participants by ensuring that a potentially impactful intervention will be available to all after a brief waiting period. While the randomised clinical trial design requires an untreated comparison group to assess efficacy of the intervention, we felt it would be unethical to deny control participants access to the intervention. While a delay in the receipt of the intervention was not ideal, we felt the ethical advantages of wait-list control design outweighed those of a treatment-as-usual comparison group. The delayed intervention phase provides an opportunity for the control arm to receive the Manas por Manas intervention and simultaneously to (a) follow intervention arm participants for an additional year to assess the persistence of intervention effects and (b) replicate main trial findings (at 1 year) using wait-list control data.

Objectives

This randomised controlled trial had the following aims:

Aim 1, *HIV testing*: to determine whether uptake of regular HIV testing, including both self-testing and clinic-based testing, is higher among trans women randomised to an intersectional stigma intervention compared with those assigned to the control condition. Aim 1a (exploratory): to explore persistence of gains in regular HIV testing among intervention arm participants following the conclusion of their participation in the intervention.

Aim 2, *HIV prevention*: to determine whether PrEP initiation and persistence are higher among trans women randomised to an intersectional stigma intervention compared with those assigned to the control condition. Secondary prevention outcomes include PrEP adherence, condom use, and utilisation of sexual health and harm reduction. Aim 2a (exploratory): to explore persistence of prevention gains post-intervention.

Aim 3, *mechanisms*: to explore changes in intersectional stigma, including reductions in internalised stigma and increased resilience to anticipated and enacted stigma, among those assigned to intervention compared with those assigned to the control arm, and assess how changes in stigma result in prevention uptake.

Trial design

Manas por Manas is being evaluated using a randomised wait-list controlled trial among 392 trans women in São Paulo, Brazil. We will compare uptake of HIV testing, PrEP use and other prevention services among those in the intervention arm compared with those in a wait-list control arm. In secondary, exploratory analyses, we will assess changes in intersectional stigma and its impact on observed differences between groups. We will also explore whether the effects of Manas por Manas persist post-intervention. We will measure PrEP use with national electronic dispensing data and drug level testing, assess HIV testing with clinic records and surveys, and measure intersectional stigma through comprehensive survey measures for 12 months post-randomisation at 3-month intervals (see figure 1 for the schedule of enrolment, intervention and assessments). This trial also includes a longitudinal qualitative cohort with a diverse subsample of 20 participants to explore how intersectional stigma impacts engagement in Manas por Manas and HIV prevention uptake, including semistructured interviews at two time points.

METHODS

Participants, interventions and outcomes

Study setting

This study is being conducted in the São Paulo metropolitan area in Southern Brazil in collaboration with the Santa Casa School of Medical Sciences (Faculdade de Ciências Médicas da Santa Casa de São Paulo). São Paulo is the largest city in Latin America, among the first to document HIV among lesbian, gay, bisexual, transgender and intersex (LGBTI) communities, and both a global leader in equity of HIV treatment and a world centre for gender transition care. Study visits are conducted at three sites located throughout the city. The state HIV care reference and training centre (CRT) includes a large outpatient

clinic for HIV/AIDS and is home to the largest and more comprehensive outpatient clinic for transgender health in the country. The second site is SAE Campos Elíseos, a public health facility in central São Paulo serving a large trans population. HIV testing, care and treatment, and PrEP are available at both clinic locations; participants who seroconvert will be referred to the specialised HIV care service of their choice for treatment. Finally, to ensure that participants who prefer not to engage with those specific clinic facilities can also participate, activities also occur at the Núcleo de Pesquisa em Direitos Humanos e Saúde da População LGBT (NUDHES) community research office in central São Paulo.

Eligibility criteria

Participants must be 18 years or older; currently identify as female but assigned 'male' at birth, transgender, transsexual or *travesti* (a common term for trans women in Brazil); not be known to be living with HIV; be a resident of the São Paulo metropolitan area; and consent for study procedures, including review of clinical records. In Brazil, language that trans women use to describe themselves includes cultural terms such as 'transsexuais', 'mulher trans' and 'travesti', among others. No restrictions are placed on the degree to which the participant has transitioned legally or physically. We did not include trans women under the age of 18 years due to ethical and safety concerns raised by needing to obtain parental consent for their participation. Obtaining parental consent for participation in a study focused on trans women's sexual health could potentially out some participants as trans to their parents and could also raise issues related to HIV and PrEP stigma. Participants may be PrEP-naïve or have initiated PrEP; being on PrEP is not an exclusion criterion.

Recruitment

Participants were recruited between 26 November 2020 and 8 June 2022. Recruitment was delayed and prolonged due to the COVID-19 pandemic, during which in-person activities were largely not possible. Many of our participants were recruited from housing shelters that serve trans women, LGBT+ non-governmental organisations and other community organisations, and primary care facilities that provide hormone therapy. We also invited trans women testing negative for HIV at either SAE Campos Elíseos, the CRT or through the community-based testing programmes run by CRT to participate. All participants provided informed consent for study procedures, including clinical record extraction and PrEP eligibility examinations (eg, HIV and creatinine) if interested in PrEP, per national guidelines.

Participant timeline

The data collection schedule includes study visits every 3 months for 24 months (see figure 2). The enrolment visit and every 6-month visit include a comprehensive survey conducted in person. At enrolment, participants provide informed consent and then respond to the first (baseline)

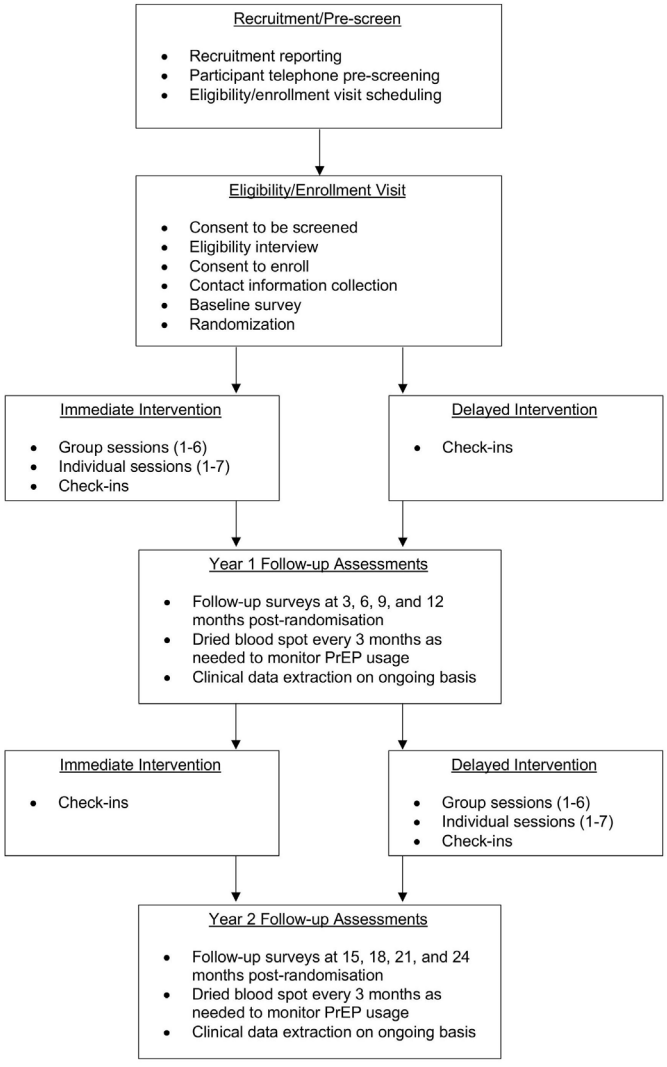

Figure 2 Schedule of enrolment, interventions and assessments (CONSORT diagram). CONSORT, Consolidated Standards of Reporting Trials; PrEP, pre-exposure prophylaxis.

comprehensive survey. Comprehensive surveys assess hypothesised covariates and mediators of our primary and secondary outcomes (see table 1). The brief (15 min) monitoring surveys (ie, 3, 9, 15 and 21 months) include abbreviated surveys that focus on capturing primary study outcomes and are conducted by phone unless the participant prefers to come to a study site. Follow-up assessments, including biomarker collection and surveys, occur for 24 months post-randomisation at 3-month intervals (for measures, see table 1). Enrolment was completed between November 2020 and June 2022. At the time of this manuscript submission (June 2023), we are finalising the baseline dataset, and we anticipate all data analyses and dissemination of primary trial results to conclude in 12 months.

Interventions

Manas por Manas is a multilevel (group-level and individual-level) intervention to improve engagement in the HIV prevention continuum among trans women

Table 1 Primary and secondary measures

Domain	Instrument/measure	Data source	Frequency of data collection/extraction
Primary exposure			
Intervention	Randomisation arm	Enrollment/study records	Continuous during enrolment
Primary outcomes			
HIV testing	Binary: tested (HIVST or at a clinic) in past 3 months	Clinical data extraction; study records (HIVST); self-report (testing)	Extracted biannually, continuous, monitoring visits (3-monthly)
PrEP initiation	Binary: initiation of PrEP in past 3 months*	National data (SICLOM); self-report	Extracted quarterly
PrEP persistence	Binary: PrEP dispensed with 80 or more days covered in 3 months per dispensation records *	National data (SICLOM)	Extracted quarterly
Secondary outcomes			
Prevention and service uptake	Uptake of harm reduction services	Self-report	Monitoring visits (3-monthly)
	STI referrals and treatment	Clinical data extraction; self-report	Extracted biannually, monitoring visits (3-monthly)
	Condom use (consistent use with regular and occasional partners and clients)	Clinical data extraction; self-report	Extracted biannually, monitoring visits (3-monthly)
PrEP adherence	Drug levels	Dried blood spots	Monitoring visits (3-monthly)
Secondary exposure			
Intervention dose	Engagement with intervention (group sessions & navigation)	Study monitoring forms	Continuous
Covariates/mediators			
Demographics	Age, gender identity, SES, race, housing stability, mobility, employment, sex work	Self-report—surveys	Comprehensive visits (6-monthly)
Intersectional stigma	*Internalised anticipated* and *enacted* stigma related to: Identity-based stigma: gender,[65] race[66] Social position-based stigma: sex work,[67] substance use Stigma-related barriers: HIV stigma[68]; PrEP stigma[69]	Self-report—surveys	Comprehensive visits (6-monthly)
	Stigma resilience: coping self-efficacy[70–72] Healthcare empowerment[73]	Self-report—surveys	Comprehensive visits (6-monthly)
Gender affirmation	Need for and experiences of gender affirmation[35] Transgender group identity[65]	Self-report—surveys	Comprehensive visits (6-monthly)
Social, structural barriers to/facilitators of prevention	Depression,[74–76] substance use,[77] social support,[78 79] social cohesion,[80 81] relationship violence,[82] trauma,[83] access to clinical care and services received, food insecurity[84 85]	Self-report—surveys	Comprehensive visits (6-monthly)

*calculated among those with indications for PrEP use.
HIVST, HIV self-testing; PrEP, pre-exposure prophylaxis; SES, socioeconomic status; SICLOM, Sistema de Controle Logístico de Medicamentos; STI, sexually transmitted infection.

in Brazil by addressing intersectional stigma, specifically identity-based stigmas related to gender identity and race, stigmas based on social position, for example, engagement in sex work and substance use, and stigma-related barriers, specifically HIV and PrEP stigma. The group-level component of Manas por Manas is facilitated by two peer navigators (PNs) and consists of six sessions conducted over 12 weeks. To address HIV stigma, some PNs are living with HIV and others are HIV negative. Group content (see table 2) is informed by the Model of Gender Affirmation and designed to address intersectional stigma through building gender pride (reducing internalised stigma), role modelling (reducing HIV and PrEP stigma), and empowering participants to access healthcare by problem-solving anticipated stigma and effectively responding to enacted stigma (increasing stigma resilience). Following the group sessions, the individual-level component of Manas por Manas consists

Table 2 Manas por Manas intervention content

Session	Topic	Objectives
1	Gender Pride/Orgulho Trans	Explore and discuss trans identities and history in Brazil Discuss gender pride, identify positive role models to combat internalised stigma Introduce HIV self-testing and PrEP in relation to the concepts of self-care, self-worth and sexual health
2	Looking Good, Feeling Good/ Sou Bonita Meu Bem, e Daí?	Discuss gender affirmation, its effect on self-image, self-care, empowerment to cope/respond to enacted stigma Discuss transition-related healthcare (ie, hormone use/access, dangers of and safer injection silicone practices) Empower access to gender-affirming healthcare, including HIV testing, PrEP or engagement in HIV treatment Explore relationship between physical health (eg, nutrition, sleep, HIV testing) and feeling good about oneself
3	Let's Talk About Sex/Vamos Falar Abertamente Sobre Sexo	Provide information on HIV rates and risk factors among trans women in Brazil Discuss self-protection in the context of gender affirmation, including HIV testing and PrEP Discuss the importance of knowing one's HIV status and getting treatment if positive Empower access to HIV testing and treatment services; discuss barriers to HIV testing and treatment, such as anticipated stigma and/or previous experiences of enacted stigma, and coping strategies (eg, HIV self-testing)
4	Taking Back the Power/Dando a Volta por Cima	Discuss how trans-related stigma impacts one's sense of personal power, explore ways to reclaim one's power to confront stigma Explore assertiveness skills, practice communicating with healthcare providers to challenge structural and interpersonal enacted and anticipated stigma
5	Surviving and Thriving/Sobrevivendo e Crescendo	Discuss how knowing one's HIV status and getting tested and/or treatment for HIV are vital to self-care Discuss healthy ways of coping with transphobic stigma in relationships and the stress of sex work Consider the effect of substance use on one's sexual health; offer harm reduction resources and support Celebrate trans community as a vital source of social support Reinforce gender pride to resist internalisation of intersectional stigma
Reunion (3 months after session 5)	Living Your Power/Vivendo o Seu Poder	Explore ongoing self-care strategies, including gender affirmation, regular HIV testing and/or PrEP persistence Review assertiveness skills and discuss experiences communicating with healthcare providers to challenge structural and interpersonal enacted and anticipated stigma Reinforce gender pride to resist internalisation of intersectional stigma
Navigation (for 7 months post-groups)	Staying Connected/Permanecendo Ligada	Provide one-on-one individualised support for navigating current healthcare system, reinforcing concepts from group work, including problem-solving and strategies for coping with anticipated and enacted stigma

PrEP, pre-exposure prophylaxis.

of 7 months of peer navigation to support HIV prevention uptake including HIV testing (clinic based or self-testing), PrEP or HIV care (if participant tests positive during the intervention), and harm reduction services for those for whom these services are indicated. The 7 months of peer navigation reaffirm strategies learnt during group sessions in one-on-one navigation sessions, with a reunion group session 3 months into individual navigation, which provides an opportunity to share experiences collectively (see table 2 for Manas por Manas intervention activities outline).

Intervention delivery training

The multiweek PN training used detailed manuals we developed for facilitating the group sessions and conducting peer navigation. For the group-level component, PNs acquired skills in group facilitation through coaching, role-plays and mock sessions. HIV-related training content included personalised HIV risk assessment, HIV test counselling (including HIV self-testing (HIVST)), PrEP and HIV treatment. Stigma-related training content included the concepts of intersectional stigma and gender affirmation, with a focus on the types of stigma targeted by the intervention (identity, social position and barriers) and building stigma resilience through coping skills (eg, coping with anticipated and enacted stigma) and empowerment. For the individual-level component, PNs are trained on the role of a PN, providing support to participants in developing

a personalised HIV prevention plan, fostering an alliance and ethical behaviour, including maintaining appropriate personal/professional boundaries. Refresher training sessions are conducted regularly to improve facilitation and navigation skills, to train new PNs if staff turnover occurs, and to address challenges.

Intervention supervision

PNs meet with the PN supervisors two times per week (once a week for one-on-one supervision and once a week for group supervision) to conduct case conferences, receive support and problem-solve. The study coordinator meets weekly with the PN supervisors, a weekly meeting with the interviewers, and has biweekly calls with investigators to discuss issues and strategise solutions. The study coordinator and the PN supervisors have biweekly meetings with the 16 PNs.

Measures

Primary exposure

Randomisation arm—intervention or wait-list control—is the primary predictor variable for all primary analyses and is conducted and captured in the REDCap system and recorded on study enrolment forms. Because the degree of engagement with the intervention varies by individual, we also capture intervention dose on study monitoring forms as a secondary exposure measure for additional (per-protocol) analyses.

HIV testing uptake is defined as any clinical evidence or report of HIV testing in each interval. This includes multiple data sources: documented HIV testing at a study clinic, report of having attended a non-study clinic for HIV testing, or evidence of HIVST kit receipt with self-report of HIVST use and/or documented HIVST use by the PN during a group or individual navigation session.

The primary PrEP use outcome measure is *PrEP persistence*, which is the PrEP measure used for sample size calculations. We document *PrEP initiation*, defined as a participant filling their first PrEP prescription, through PrEP dispensing information in the national SICLOM (Sistema de Controle Logístico de Medicamentos) database. However, because initiation does not imply continued use, we focus analyses of PrEP use on *PrEP persistence*—or documented use at every interval, defined as sufficient pill dispensation for complete 3-month coverage with no more than 10 days uncovered in the period. Secondary outcomes, including *PrEP adherence* and uptake of other prevention services (harm reduction, sexually transmitted infection (STI) care), are listed in table 1.

Mediators: intersectional stigma

We include a comprehensive suite of stigma measures that will be examined together in mediation and moderation analyses. To explore the concept of intersectional stigma, we will analyse potential interactions between the stigma domains. This reflects the concept of intersectionality as more than an additive process of multiple stigmatised identities, but where experiences of multiple types of stigma create a confluence of interlocking systems of oppression that act synergistically as barriers to prevention and cannot be meaningfully interpreted independently. We include quantitative measures of internalised, anticipated and enacted stigma in the following domains: gender-related stigma, race-related stigma, stigma related to sex work and substance use, HIV and PrEP stigma. Stigma resilience is operationalised as coping self-efficacy and healthcare empowerment in the context of stigma. Comprehensive surveys are conducted at enrolment and at 6-month intervals until endline.

Covariates

We measure demographic and other individual, social, and structural barriers or facilitators to care to assess potential covariates and confounders in analyses.

Sample size

Based on α=0.05 and power=0.80, given the sample size of 392, anticipating 25% attrition and also accounting for a range of possible correlations between participants receiving the intervention from the same PN pairs, we will have sufficient power to detect even small-to-medium effects, including effects as low as 13% and 8% difference in proportion of HIV testing and persistent PrEP use, respectively. This difference represents more than a doubling of PrEP use in the intervention arm as compared with control. We expect HIV prevention outcomes to improve in the intervention group relative to the control group during the main trial phase. We hypothesise that, following the intervention, the odds of HIV testing and persistent PrEP use will be higher for intervention participants relative to control participants. Our primary interest is to estimate the marginal or population average effects of intervention participation on these primary outcomes rather than the effect for a hypothetical average subject. Accordingly, generalised estimating equations (GEE) will be used for the primary analyses to test our hypotheses via time-averaged comparisons of post-baseline (follow-up) measurements of the intervention group with the control group in the main trial phase. GEE will also be used to test our hypotheses that following the intervention, relative to the control arm, intervention arm participants will have: (1) higher mean levels of resilience to anticipated stigma, (2) higher mean levels of resilience to enacted stigma and (3) lower mean levels of internalised stigma.

Patient and public involvement

The development of the Manas por Manas intervention and the implementation of the RCT were informed by a Community Advisory Board (CAB) comprised of seven transgender women, including participants from previous studies, activists, leaders of LGBT organisations and health workers. The CAB also developed the visual identity of the project, including choosing the name, images/logo and colours, in collaboration with three local graphic designers.

Assignment of interventions

Allocation

Sequence generation

The US-based study statistician generated the randomisation scheme using SAS V.9.4 via randomly permuted blocks using a 1:1 allocation to either Manas por Manas or wait-list control condition.

Implementation

The resulting allocation list was stored in the REDCap electronic data capture tool, hosted at the University of California, San Francisco (UCSF). REDCap is a secure, web-based software platform designed to support validated data capture for research studies.[36 37] All three study sites drew from a single randomisation list. The site research team and the investigators did not have access to the randomisation scheme at any time. At the time a participant was consented and enrolled into the study, REDCap assigned the next available randomisation status to the participant's electronic record. The research assistants informed participants of their assigned study arm at the end of the enrolment visit.

Concealment mechanism

Allocation concealment was ensured, as the randomisation procedure did not release the randomisation code (to participants or study staff) until the participant had been enrolled into the trial and all baseline measurements had been completed.

Blinding

Blinding was not used in this trial as assignment needed to be known by the study team to carry out the intervention. Outcome assessors (study interviewers) were not blinded because they informed participants of their study condition assignment. PNs did not serve as outcome assessors.

Data collection, management and analysis

Data collection methods

All surveys are interviewer administered on encrypted study laptops with the interviewer inputting responses directly into REDCap. Participants are reimbursed for all study visits. Participants may choose to schedule visits at any of the three project sites to optimise convenience. For those on PrEP, data collection visits are scheduled at the participant's clinic to ensure that PrEP distribution, HIV testing, dried blood spot (DBS) collection and survey data collection are integrated efficiently into clinical care. Study staff are available at each site. For participants with difficulty presenting at a study location for comprehensive surveys, staff offer the survey by phone or WhatsApp to minimise missing data, though attempts are made to maximise in-person data collection.

Primary outcome

PrEP data extraction

Data regarding PrEP use, which became available nationally for at-risk populations in December 2017, are extracted from the national SICLOM database, which captures all antiretroviral distribution nationally. PrEP dispensing data are extracted quarterly from SICLOM and stored securely, including visit dates, pill count and dose, and any associated observations. We use clinical records at the facilities to note visits for other purposes, including visits related to PrEP side effects.

Clinic data extraction

Clinic-based HIV testing data and uptake of clinic-based prevention services, including STI testing and treatment, sexual health counselling and HIV care visits (for those who seroconvert) are extracted biannually, including visit purpose, dates, services received, HIV test result and associated observations. Data from participant clinical files are extracted electronically and uploaded to a secure database kept by the study data managers.

DBS collection and drug concentration testing

Drug concentrations in the blood measured using DBSs have emerged as strong correlates of protection in PrEP trials, accounting for most of the variation in PrEP benefits. For participants who report current PrEP use, DBSs are collected at the clinical sites at each visit by trained staff and processed in accordance with standard procedures. Staff use a medium-gauge lancet to puncture the fingertip and extract whole blood onto filter paper, to be dried on a storage rack prior to placing the DBS in individual plastic zip lock bags with a desiccant packet and humidity indicator. DBSs are temporarily stored at each clinic in a freezer at −20°C, and are shipped and tested using a validated method for quantification of drug concentrations of tenofovir and emtricitabine.[38] Drug concentration testing is performed by the Colorado Antiviral Pharmacology Laboratory at the Skaggs School of Pharmacy and Pharmaceutical Sciences at University of Colorado, Denver. Adherence is defined as having drug concentrations at levels required for protection (≥4 pills per week).[39]

Retention

To ensure the best possible retention, we will collect cell phone information for retention and follow-up procedures at the first (enrolment) study visit and confirm and/or update all contact information at each subsequent visit. The staff who conducts recruitment and enrolment will also text the participant (via SMS or WhatsApp, depending on the participant's preference) to ensure the phone number provided is working prior to completion of enrolment procedures. We will collect additional contact information, including alternative contacts and participant preferences for contact at the time of enrolment, to ensure multiple avenues for follow-up. We will offer participants the opportunity to conduct their follow-up visits (every 3 months) at any of the three study sites to provide the most convenient location and will provide a small reimbursement to ensure that costs to arrive at the chosen study site are compensated.

To optimise retention for all follow-up visits, study staff will text (or WhatsApp or contact via Facebook) all participants 1 week and 1 day prior to their follow-up visits to remind them of the date and time they agreed to come in. Those who do not confirm or attend their scheduled visits will be contacted (phoned and/or texted) to remind them of the missed appointment and reschedule. We will attempt up to five contacts and attempts to reschedule for each study visit. After five attempts, if the individual is not responsive, the visit will be considered 'missed' and attempts for the following visit (3 months later) will resume 1 week prior to the next visit. Because mobility is an issue in this population, non-response will not be considered tacit refusal in perpetuity. In our previous studies, some participants did not respond to contact and then resumed contact following visits away from the area. As a result, only participants who explicitly state that they would like to withdraw will no longer be contacted by the study.

Data management

All data are password protected and stored on an encrypted secure server. Participants' identity and data are handled with highest levels of care and confidentiality. The information provided by participants is coded with a unique study number to protect privacy. Only study staff has access to participant data. Other entities who may access research data include UCSF Committee on Human Research; National Institutes of Health (NIH); University of California; and the Comitês de Ética em Pesquisa/Comissão Nacional de Ética em Pesquisa (CONEP) system of ethical regulation in Brazil.

Statistical methods

Preliminary analyses and missing data

Frequency tables for all variables and measures of central tendency and variability for continuous variables (eg, stigma scores) will characterise the sample and will be stratified by randomisation arm to check for imbalances. If arms differ significantly at baseline on one or more covariates, we will use causal modelling methods (eg, targeted maximum likelihood estimation) to obtain the desired marginal effect estimates under the counterfactual assumption of balanced arms.[40–44] We will address incomplete data with multiple imputation (MI)[45]; MI makes the relatively mild assumption that incomplete data arise from a conditionally missing-at-random (MAR) mechanism.[46] Auxiliary variables will be included to help meet the MAR assumption[47 48] and sensitivity analyses will be conducted with weighted MI[49] to assess the robustness of the MAR assumption.[50] SAS V.9.0[51] and M*plus*[52] will be used for primary analyses.

Primary analyses for specific aims 1 and 2

Our primary analyses for aims 1 and 2 will follow an intent-to-treat (ITT) approach by including all randomised participants in the analyses, even if they do not complete all study measurements. We will examine the effects of the intervention on HIV testing and prevention use (PrEP persistence) by comparing outcomes in those randomised to the intervention as compared with those randomised to a control condition. In order to test our primary hypothesis for aim 1, that the odds of HIV testing will be higher for participants in the intervention arm relative to participants in the control arm, and for aim 2, that the odds of persistent PrEP use will be higher for participants in the intervention arm relative to participants in the control arm, we will use GEE. Our primary interest is to estimate the marginal or population average effects of intervention participation on these primary outcomes rather than the effect for a hypothetical average subject.[53] Moreover, within-subject outcome correlations are considered nuisance parameters rather than quantities of interest to be modelled explicitly. Accordingly, GEE can be used to estimate the marginal effects using time-averaged comparisons of post-baseline (follow-up) measurements of the intervention group with the control group in the main trial phase. α will be set at 0.05 for these two planned comparisons. Any additional post-hoc comparisons (eg, paired comparisons of groups at each time point) will maintain a nominal α of 0.05 through the use of simulation-based stepdown multiple comparison methods.[54]

Though GEE estimates are consistent even if the correlation structure is misspecified, GEE's statistical efficiency improves as the working correlation structure more closely approximates the actual correlation structure[55]; therefore, various correlation structures suitable for the study's design will be considered (eg, exchangeable; *M*-dependent).[56] The QIC statistic will be used to select the final correlation structure.[57] Additional covariates such as baseline stigma measures will be included if they improve QIC. Robust Huber-White 'sandwich' SEs will be used to obtain correct inferences even if the chosen correlation structure remains slightly misspecified.

Statistical power analysis for specific aims 1 and 2

Power analyses were generated using the two-group repeated proportions module in NCSS PASS V.16[58] to compute minimum detectable effect sizes for the primary analyses to address hypotheses 1 and 2. Accounting for 25% potential attrition, the study will begin with 400 participants, but power calculations are based on complete data from 300 participants only for analysis. Furthermore, although we will make every possible effort to standardise intervention delivery, it is possible that observations from participants who receive intervention from the same Manas por Manas PN pairs will be positively correlated. Accordingly, we lowered the effective sample size (ESS) input for the power analyses to be ESS=N/DEFF, where DEFF is the design effect or variance inflation attributable to using correlated data, calculated as $1+(m-1)\times ICC$ where m is the average number of participants per PN pair and ICC is the intraclass correlation within PN pairs. Since this ICC and the within-subject correlation of observations within participants, ρ, are unknown, we assumed a range of plausible values for ICC and ρ. Assuming

Table 3 Minimum detectable effect sizes for primary hypotheses 1–3 for specific aims 1–3

		ICC=0.0125			ICC=0.025			ICC=0.0375			ICC=0.05		
Specific aim 1	**ρ**	**OR**	**Pdiff**	**h**	**OR**	**Pdiff**	**h**	**OR**	**Pdiff**	**h**	**OR**	**Pdiff**	**h**
HIV testing	0.20	1.69	12.9%	0.261	1.86	15.1%	0.307	2.03	17.0%	0.347	2.19	18.7%	0.383
(P_0=0.50)	0.30	1.78	14.0%	0.284	1.98	16.4%	0.334	2.18	18.5%	0.379	2.36	20.3%	0.418
	0.40	1.86	15.0%	0.305	2.09	17.6%	0.360	2.32	19.8%	0.407	2.53	21.7%	0.449
	0.50	1.94	16.0%	0.326	2.19	18.7%	0.383	2.46	21.1%	0.436	2.71	23.0%	0.478
Specific aim 2	**ρ**	**OR**	**Pdiff**	**h**	**OR**	**Pdiff**	**h**	**OR**	**Pdiff**	**h**	**OR**	**Pdiff**	**h**
PrEP use	0.20	2.66	7.3%	0.266	3.08	8.9%	0.313	3.48	10.5%	0.358	3.85	11.9%	0.396
(P_0=0.05)	0.30	2.86	8.1%	0.290	3.34	10.0%	0.344	3.81	11.7%	0.391	4.25	13.3%	0.433
	0.40	3.06	8.9%	0.313	3.60	10.9%	0.369	4.14	12.9%	0.423	4.63	14.6%	0.466
	0.50	3.25	9.6%	0.333	3.86	11.9%	0.396	4.46	14.0%	0.451	5.02	15.9%	0.499
Specific aim 3	**ρ**			**d**			**d**			**d**			**d**
Stigma	0.20			0.260			0.306			0.347			0.382
	0.30			0.283			0.334			0.379			0.416
	0.40			0.305			0.359			0.407			0.448
	0.50			0.325			0.383			0.434			0.478

ICC, intraclass correlation; PrEP, pre-exposure prophylaxis.

α=0.05 and power=0.80, we computed the minimum detectable OR, proportion difference (*pdiff*) and standardised proportion difference (*h*) for the proposed time-averaged comparisons, assuming four post-baseline measurements at 3, 6, 9 and 12 months and assuming control group proportions P_0=0.50 for HIV testing and P_0=0.05 for PrEP use based on preliminary data from our in-country partners. Effect size estimates for our primary analyses fall between cut-offs of 0.20 and 0.50 for small and medium standardised effect sizes,[59] respectively, suggesting that primary analyses have sufficient power to detect small-to-medium effects across a variety of conditions (table 3).

Primary analyses: aim 3

GEE will be used to test hypotheses to fulfil specific aim 3 following the same modelling approach as described above for specific aims 1 and 2, except that a normal distribution and identity link will be employed to analyse continuous, normally distributed stigma scores. We hypothesise that following the intervention, relative to the control arm, intervention arm participants will have: (1) higher mean levels of resilience to anticipated stigma, (2) higher mean levels of resilience to enacted stigma and (3) lower mean levels of internalised stigma. As for aims 1 and 2, these hypotheses will be tested via planned time-averaged comparisons of post-baseline measurements of the intervention arm with the control arm in the main trial phase. These comparisons will be tested at α=0.05 per comparison. As in aims 1 and 2, these analyses will follow an ITT approach.

Statistical power analysis for specific aim 3

Power analyses were generated using the two-group repeated means module in NCSS PASS V.16[58] to compute minimum detectable effect sizes for the primary analyses to test the three hypotheses proposed to address specific aim 3. As noted above, the study will begin with 392 participants equally allocated to the two study arms and we are assuming 25% attrition, yielding data from 294 participants for analysis at all time points. We have also adjusted the ESS due to correlation of data from participants with the same PN pair, using an ESS input for the power analyses that is ESS=N/DEFF, where DEFF is the design effect or variance inflation attributable to using correlated data, calculated as $1+(m-1)\times ICC$ where m is the average number of participants per PN pair. ICC is the intraclass correlation within PN group pairs (group leaders). Since this ICC and the within-subject correlation of observations within participants, ρ, are unknown, we assumed a range of plausible values for ICC (0.0125–0.05) and ρ (0.2–0.5). Assuming α=0.05 and power=0.80, we computed the minimum detectable standardised mean difference *d* for the proposed time-averaged comparisons, assuming four post-baseline measurements at 3, 6, 9 and 12 months in the main trial phase and assuming continuous normal stigma outcome measures. Effect size estimates for our aim 3 primary analyses fall between cut-offs of 0.20 and 0.50 for small and medium standardised effect sizes, respectively,[60] suggesting that primary analyses have sufficient power to detect small-to-medium differences in mean stigma and resilience measures.

Monitoring

Data monitoring

Recruitment goals, missing data and follow-up failures are monitored monthly throughout the trial.

Formal committee

The study's Data and Safety Monitoring Board (DSMB) is independent from the sponsor; members do not have

any competing interests. Board members were chosen for their relevant expertise on study content, target populations and methodologies. The roles of our DSMB include: reviewing analyses of outcome data and data safety to determine whether the trial should continue as originally designed, should be changed or should be terminated based on these data; reviewing trial performance information, such as accrual information; determining whether and to whom results should be released prior to the reporting of the study results; reviewing reports of related studies to determine whether the monitored study needs to be changed or terminated; and reviewing major proposed modifications to the study prior to their implementation.

Harms

All safety-related risks of harm are monitored routinely at the time of the assessment or intervention session. The security of confidential information is monitored regularly. Study staff are trained in asking questions about sensitive topics in a caring and non-threatening manner and stopping questioning at the first sign of discomfort or on request. Privacy, confidentiality and disclosure comfort are emphasised in every session. Group facilitators request that participants agree to respect the privacy and confidentiality of other members of the group and to not disclose anyone's personal information to anyone outside of the group. Participants are informed that assessment responses are kept confidential and are not used against them in any manner. Study staff are trained to identify any participant distress. For participants who report distress or suicidality, a protocol guides staff action, including steps to assess the level of distress, to obtain emergency contact information for clinical supervisors and to obtain up-to-date phone numbers for crisis centres, hotlines and referral agencies.

Study staff are trained to report breach of confidentiality risks incurred by participants to the project director, who in turn was trained to inform the principal investigators (PIs). Any participant in need of treatment due to distress is referred for appropriate services after staff followed the participant distress protocol and inform the project director and PIs. Finally, the PIs are responsible for informing the DSMB chair, Institutional Review Board (IRB) through the IRB adverse event reporting procedure and the sponsor project officer through immediate email of any life-threatening incidents and through annual reports of other incidents. The PIs are prepared to take appropriate action to stop the study, release a participant from the study, or modify procedures to reduce and/or eliminate the above-mentioned risks if they occur at an unacceptable level.

Interim analysis

No interim analyses will take place during the trial.

Auditing

No trial audits were planned or conducted, but participating institutions had the authority to perform random audits of research protocols.

DISCUSSION

Manas por Manas is the first multilevel, multicomponent intervention designed specifically to increase HIV prevention uptake, namely HIV testing and PrEP, by reducing the impact of intersectional stigma among trans women, the group at highest risk of HIV acquisition in Brazil and globally. By integrating several evidence-based intervention components, all of which are feasible and acceptable in the target population, and all of which have evidence of efficacy with at-risk populations, this project is uniquely poised to demonstrate the first evidence-based approach to improving the HIV prevention continuum among trans women through the lens of intersectional stigma.

Our conceptual framework for the intervention, the Model of Gender Affirmation, developed by multi-PI Dr Sevelius and adapted for the Brazilian context by the project staff, uniquely addresses the lived experiences of trans women. Many HIV prevention interventions either subsume trans women under the category of 'men who have sex with men (MSM)' or attempt to adapt approaches that were developed for MSM to apply to trans women. Current best practices for public health research with trans women emphasise that trans women experience a unique social context and intersectional stigma impacts that cannot be accounted for by interventions that were developed for MSM.[61–63] Our intervention approaches represent decades of trans-specific research and intervention development and testing, and does so in an urban setting with large numbers of transgender women, in a context where PrEP and HIVST are available publicly.

In addition, our study design, measurement and analytical approach reflect the concept of intersectionality as more than an additive process of multiple stigmatised identities, recognising that experiences of multiple types of stigma create a confluence that results in interlocking systems of oppression that cannot be meaningfully interpreted independently. For this reason, we will explore the confluence of stigmas quantitatively, assessing moderation or interaction of identity-based and social position-based stigma as well as stigma-related barriers to prevention. We will also collect longitudinal qualitative data designed to elucidate how social and structural processes of intersectional stigma evolve over time and within the context of the intervention. This study contributes to gaps in understanding how intersectional stigma impacts uptake of HIV prevention and provide insights regarding measurement and mechanisms of effect in an evolving field of study. In addition to the multilevel intervention described here, structural interventions are urgently necessary to improve HIV care outcomes among transgender women in Brazil.[64]

This multilevel intervention is the culmination of years of our collaborative work in trans-specific HIV prevention interventions and a novel conceptual framework unique to trans women. Trans women in Brazil suffer an HIV burden over 50 times that of other groups.[17] Agencies and community leaders are rightfully demanding efficacious interventions to curb the devastating impact of HIV on trans communities. This study balances this impassioned outcry for urgent action with the measured, scientific rigour necessary to confidently and ethically evaluate the efficacy of this highly promising approach to reducing intersectional stigma to improve the HIV prevention continuum among transgender women in Brazil.

ETHICS AND DISSEMINATION

Research ethics approval

This study was reviewed and approved by the UCSF IRB (19-28379) and CONEP (Research Ethics National Commission, CAAE: 25215219.8.0000.5479) in Brazil.

Consent or assent

Participants expressing interest are screened for eligibility. All participants must be able to provide informed consent. Consent is obtained in Portuguese in a private location; the consent form is read to each participant and explained to them by the study staff. We confirm that participants understand material covered in the consent form by asking questions prior to their signing, for example, 'Can you tell me what will happen if you participate in the study?' If interviewers assess that the participant's level of understanding is insufficient and cannot be addressed by additional clarification, the participant is excluded from the study and provided with appropriate referrals. If the research staff person conducting the informed consent process feels there is a question about the need for more formal assessments of the decisional capacity of a potential participant, she contacts her supervisor. Interviewers witness and date the consent after the participant signs.

Confidentiality

The following confidentiality protection steps were implemented: study staff participated in training, ongoing monitoring and supervision to ensure understanding of the ethical issues involved in this research; only trained staff knew the name, identification number and contact information of participants; consent forms were kept in locked files; personal identifiers linked to data were removed and replaced by code numbers in all records. Electronic copies of data were stored on a secure password-protected server. Paper copies of data will be destroyed at the end of the study.

Dissemination policy

Trial results

Following study completion and publication of primary reports, research data will be shared in accordance with NIH guidelines (http://grants.nih.gov/grants/policy/data_sharing/). As PIs, Drs Sevelius and Lippman share information about this trial via timely registration and updates in ClinicalTrials.gov and will provide results in accordance with NIH policy. The results will be published and provided in peer-reviewed academic journals and scientific presentations at national conferences. We will make our results available to the community of researchers and general public interested in transgender health to avoid unintentional duplication of research, as well as to others in the health and social services community, including HIV clinics, LGBT community-based organisations and AIDS service organisations.

Authorship

The investigators of the study will follow International Committee of Medical Journal Editors guidelines for determining authorship eligibility and order. Final authorship decisions will be made by the PIs. No professional writers will be used.

Reproducible research

We will share protocols and study forms in response to specific requests. Requests for study data will be evaluated on an individual basis, and de-identified study data will be made available as appropriate only after publication of all study outcome analyses.

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Contributors JS, SAL and MASMV conceived of the trial and designed the study. JS compiled the first draft of the study protocol manuscript. The organisational structure and responsibilities of this study include the following individuals: multiprincipal investigators JS and SAL and site principal investigator MASMV are the lead investigators and are responsible for study design; study planning; preparation of protocol and revisions; organising the Data Safety Monitoring Board (DSMB); preparation and publication of study reports; reviewing study progress;

assistance with ethics review and approval; data verification; identification and recruitment of potential participants; data collection; participant follow-up and safety; and adherence to study protocol. Co-investigator TBN was responsible for conceiving and executing the statistical analyses as the study statistician. Data managers ARM and KCB are responsible for the development and maintenance of the trial data collection and storage system, data entry, data verification and assisting with data analysis. Project directors GS and JLG are responsible for staff training and supervision, standard operating procedure development and implementation, participant randomisation and maintaining accurate reports to the sponsor, IRB and DSMB and day-to-day trial oversight. Interviewers Daniel Barros, Marilda Martins, Cintia Spindola and Fabiola Rocha are responsible for overseeing participant screening, informed consent and data collection; participant tracking; and the storage, tracking and processing of biospecimens. All authors contributed to the manuscript and consented to its final publication.

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Competing interests None declared.

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