2. SPECIFIC AIMS

Globally, transgender ('trans') women experience extreme social and economic marginalization due to intersectional stigma[1-3], defined as the confluence of stigma that results from the intersection of social identities and positions among those who are multiply oppressed[4]. Among trans women, gender- and race -based stigma intersect with social positions such as engagement in sex work and substance use[5,6], generating a social context of increased vulnerability and HIV risk[7]. In Brazil, trans women are the 'most-at-risk' group for HIV[8], with 55 times higher odds of HIV infection than the general population[9]; further, uptake of HIV testing and pre-exposure prophylaxis (PrEP) among trans women is significantly lower than other at-risk groups[10,11].

Our team has developed the only trans-specific conceptual framework, gender affirmation theory[12], to describe intersectional stigma faced by trans women, to frame investigations of how intersectional stigma results in health disparities, and to develop and test interventions to address intersectional stigma among trans women. Informed by gender affirmation theory, we propose to test a multi-level intervention to mitigate intersectional stigma and thereby increase HIV prevention uptake (HIV testing and PrEP use) among Brazilian trans women. The proposed multi-level intervention, '*Guerreiras'* ('warrior women', as named by trans women participants in Brazil), represents decades of our HIV prevention research, including HIV self-testing (HIVST)[13-18] and PrEP implementation with trans women[19-21], by our collaborative team in the United States (US) and Brazil.

The *Guerreiras* intervention is an integration of a suite of evidence-informed interventions and HIV prevention strategies, all of which have demonstrated feasibility and acceptability by trans women in Brazil, to increase self-care and reduce the negative health impacts of stigma. *Guerreiras* works at both the group- and individual-level, comprised of two intervention components: 1) a group-level, peer-led intervention, which first demonstrated efficacy with trans women in the US as '*Sheroes*'[22] and has been successfully adapted for Brazil, and 2) an individual-level peer navigation program, which is proving feasible and acceptable in current research with trans women in Brazil, and has demonstrated efficacy in other contexts[23]. At the group-level, highly trained peer navigators (PNs) will facilitate five group sessions with trans women using a manualized curriculum to address intersectional stigma and support HIV prevention uptake. At the individual-level, for six months following group sessions, the PNs will support participants one-on-one to engage in appropriate HIV prevention services (i.e. HIVST or clinic testing, PrEP, harm reduction, or HIV treatment if they test positive).

Guerreiras will be evaluated using a randomized wait-list controlled trial among 400 trans women recruited from clinics, outreach events, and an ongoing observational cohort in São Paulo. We will compare uptake of HIV testing (self-testing and clinic-based), PrEP use, and other prevention services (e.g. harm reduction) among those in the intervention arm compared to those in a wait-list control arm. We will assess changes in intersectional stigma and its impact on observed differences between groups. We will also explore whether the effects of *Guerreiras* persist post-intervention. Longitudinal qualitative data collection with a diverse subsample will explore how intersectional stigma impacts engagement in *Guerreiras* and HIV prevention uptake. We will measure PrEP use with national electronic dispensing data and drug level testing, assess HIV testing with clinic records and surveys, and intersectional stigma through comprehensive survey measures. Aims include:

Aim 1, *HIV TESTING*: To determine whether uptake of regular **HIV testing**, including both self- and clinic-based testing, is higher among trans women randomized to an intersectional stigma intervention compared to those assigned to the control condition. Aim 2a (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** is higher among trans women randomized to an intersectional stigma intervention compared to those assigned to the control condition. Secondary prevention outcomes include PrEP adherence, condom use, and utilization of sexual health and harm reduction. Aim 2b (exploratory): To explore persistence of prevention gains post-intervention.

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

This study leverages 1) a productive multi-disciplinary HIV research partnership bringing extensive experience working with trans women in Brazil; 2) multi-level intervention components with demonstrated feasibility and acceptability by Brazilian trans women, informed by gender affirmation theory designed to address intersectional stigma; and 3) a context where PrEP and HIVST are available publicly, providing an opportunity to evaluate and scale-up an HIV prevention initiative in a key health disparity population, while contributing to nascent research in intersectional stigma.

3. RESEARCH STRATEGY

3.1 Significance

Transgender ('trans') women have some of the highest rates of HIV in the world and are the highest HIV risk group in Brazil. A recent meta-analysis of pooled data among trans women from ten low-income countries found a 50-times increased odds of HIV infection compared with other adults and an HIV prevalence of 18%[1]. In South America, HIV prevalence estimates as high as 30% have been documented in population-based studies among trans women[24]. One cross-sectional study of 284 trans women in southern Brazil (1997–2014) found 25% living with HIV. In Rio de Janeiro, 31% of trans women recruited through respondent-driven sampling were HIV-positive, 7% were new diagnoses; almost one-third (29%) of their participants had not been previously tested [25]. Additional data corroborate that trans women are the 'most-at-risk' group in Brazil[8], with an estimated odds of HIV infection among trans women over 55 times higher than the general Brazilian population [9], placing Brazil among countries with the greatest HIV disparities[1].

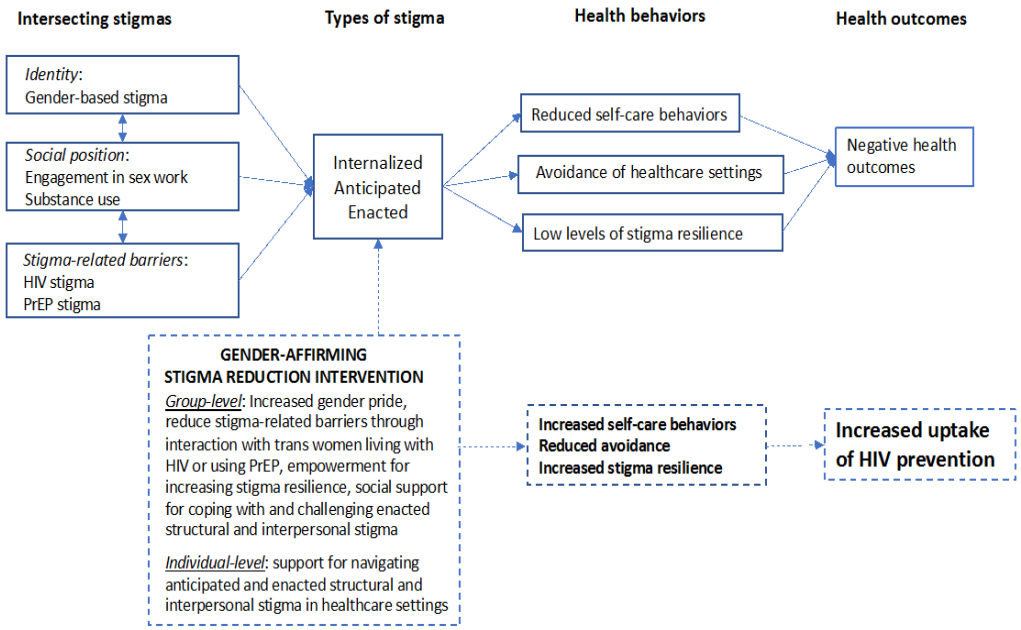
Despite high rates of HIV, HIV testing and uptake of pre-exposure prophylaxis (PrEP) among trans women is significantly lower than other at-risk groups. Trans women report multiple types of risky activities, including unprotected anal sex with multiple partners[26,27], high number of sex partners[28], sex while using drugs and alcohol[29], and sex work[30,31], yet they frequently underestimate their risk of acquiring HIV[26] and have low rates of HIV testing[32]. Further, while oral PrEP has been shown to reduce risk of HIV infection by 92% among adherent users[33], uptake of and adherence to PrEP among trans women is significantly lower than other at-risk groups[21]. In Brazil, awareness of PrEP is low among trans women despite its free availability through the Brazilian universal health system or *Sistema Unico de Saude (SUS)*[34]. One study in Rio de Janeiro found that among 345 HIV-negative trans women, 76% were willing to use PrEP once they were aware of it and 67% met PrEP behavioral eligibility criteria[35]. Despite eligibility and willingness to use PrEP, as of August 2018, only 74 Brazilian trans women had actually initiated PrEP through SUS nationally[36]. The São Paulo state PrEP monitoring report notes a need to find new strategies to attract transgender populations to PrEP .[37]

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, marginalizes stigmatized individuals, and creates a social hierarchy that reinforces social inequality[38]. Stigma is a fundamental cause of health disparities[39]. **Intersectionality** is a theoretical approach that highlights how multiple types of oppression intersect to create and reinforce social inequalities[4]. Thus, **intersectional stigma** is defined here as *the confluence of multiple stigmatized identities, social positions, and stigma-related barriers that result in structural inequalities and health disparities*[4]. Due to gender-based stigma, trans women face extreme social and economic marginalization that lead to additional stigmas based on social positions, such as engagement in sex work and substance use[6,10], which also intersect with race-based stigma. Further, these identity- and social position-based stigmas intersect with *stigma-related barriers* such as PrEP stigma[40] and HIV stigma[41] to drive low rates of HIV testing, PrEP uptake and PrEP persistence among trans women. Experiences of *enacted stigma* (experiences of being stigmatized 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 *internalization of stigma*[42] (adopting stigmatizing 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 internalization of stigmatizing beliefs[3,43,44], which includes being empowered in one's healthcare[45] despite the context of stigma.

Multi-level 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 *Guerreiras*, 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 important for long-term social change, it is also critical to increase stigma resilience among trans women through support and empowerment that is urgently necessary to navigate existing systems of care that cannot be immediately reformed and where stigma is pervasively enacted against transgender people[46,47] and continues to fuel HIV transmission[2]. 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[38,48]. Furthermore, in Brazil, where trans women experience the highest rates of violence globally despite legislative protections for the LGBQT+ population[49], the hostile political climate and current backlash against protections for marginalized populations makes this programming even more urgent. Our proposal considered a clear

priority and supported by Municipal, State, and National HIV/AIDS programs (See Letters of support).

Figure 1. Conceptual model for intersectional stigma reduction intervention



Conceptual Framework: Our multi-level *Guerreiras* intervention is informed by an innovative, transgender-specific theoretical model, gender affirmation theory[50], that addresses intersectional stigma. MPI Dr. Sevelius has developed and tested a conceptual model that examines how intersectional stigma contributes to health disparities among trans women. Gender affirmation theory integrates objectification theory[51,52] with the identity threat model of stigma[53], and draws on research examining risk as an outcome of social oppression[54]. 'Gender affirmation' refers to an interpersonal, interactive process whereby a person receives social recognition and support for their gender identity and expression. Gender affirmation theory posits that in the context of intersectional stigma[53,55], trans women attempt to reduce their experience of stigma by avoiding stigmatizing environments (e.g. healthcare settings) and undervaluing important health seeking behaviors (e.g. HIV testing, PrEP use) [55]. Research has found that gender affirmation moderates the relationship between stigma and poor health outcomes[56]. Meeting trans women's needs for gender affirmation, such as through gender-affirming relationships, decreases avoidance behavior and increases self-care and healthcare-seeking behavior, such as accessing HIV prevention services[55,57,58]. Peer networks and support are a primary source of information about PrEP, HIV testing, and safer sex behavior, while family and institutions are often stress factors[59,60]. Thus, peer-led interventions are critical for interventions that seek to reduce internalized stigma and increase stigma resilience for coping with anticipated and enacted stigma[42].

3.1.a Investigative team. Our research team brings extensive expertise in addressing intersectional stigma within HIV research with trans women, peer navigation of patients, community outreach and cohort retention in Brazil, and interdisciplinary mixed methods research. The team is co-led by UCSF Associate Professors, **Drs. Sheri Lippman and Jae Sevelius. Dr. Lippman** is an epidemiologist with long-standing collaborations in Brazil, where she conducted her dissertation on combination HIV prevention with sex workers, including trans women. Dr. Lippman, led the first study to explore use of HIV self-testing (HIVST) among trans women in the US; worked extensively on HIVST research in Brazil; has led multiple randomized trials, including the I-Care trial of peer navigation (NCT02417233) and a cluster randomized trial of community mobilization to promote testing and engagement in care in South Africa (R01MH103198); and is PI of the Trans Amigas peer navigation intervention (R34MH112177) in São Paulo. **Dr. Jae Sevelius,** a licensed clinical psychologist, is co-founder of the UCSF Center of Excellence for Transgender Health and has led or collaborated on over 30 studies focused on developing and testing some of the only evidence-based social-behavioral interventions for trans women to date. She is currently leading 2 NIH-funded efficacy trials of HIV interventions for trans women (1R01MH106373, R01MH115765) and the first trans-specific PrEP demonstration project. Dr. Sevelius led the feasibility and acceptability trials of Sheroes (1R34MH102109), the Sheroes adaptation for Brazil, and Girlfriends Connect (1R34DA038541). Dr. Sevelius was co-I on Dr. Lippman's studies of HIVST among trans women and Trans Amigas. Dr. Lippman has collaborated for over 15 years with Brazilian site PI **Dr. Maria Amelia Veras**, MD, PhD, Professor of Collective Health at Santa Casa School of Public Health. Dr. Veras is a physician epidemiologist with over 25 years of experience in HIV prevention and care research and is site PI of Trans Amigas and Trans*National (R01MD010678). She leads the multidisciplinary LGBTI (Lesbian Gay Bisexual Transgender and Intersex) Human Rights and Health Study Group (NUDHES), and has extensive experience with LGBTI community-based research in Brazil. **Dr. Gustavo Saggese,** Post-Doctorate

Researcher and early career investigator at Santa Casa, holds a PhD in anthropology and has over 10 years of experience conducting qualitative research among LGBTI populations. Dr. Saggese was the site PI of the adaptation and pilot testing of Sheroes in Brazil. Our team is uniquely positioned to lead this urgently needed research on intersectional stigma to improve HIV prevention among Brazilian trans women.

3.1.b Preliminary Studies. Our team has conducted extensive preliminary research to inform this application. While there is additional research that provides groundwork for the strategies utilized here, our team has been leading the field to shape trans-specific HIV prevention research globally and in Brazil, as outlined below.

Optimizing HIV programming for trans women in Brazil. To understand trans-specific HIV prevention and care needs in Brazil, our team conducted formative research in 2015 including focus groups with HIV-negative and positive trans women and local stakeholders to explore intervention needs and preferences[2]. Trans women and stakeholders alike advocated for peer-based support programs to address marginalization from both health and social services and to improve uptake of HIV prevention, HIV treatment, and complementary services. Key informants emphasized the need for empowerment-based, gender-affirming programming and skills building for successful engagement in health systems, including stigma resilience.

Table 1. Preliminary studies conducted by investigative team

Preliminary studies		Population	Location	Investigators
Multi-level *Guerreiras* intervention components				
Group-level: Sheroes	Feasibility & acceptability	Trans women, any HIV status	US, Brazil	Sevelius (PI)[22], Lippman, Veras, Saggese
	Efficacy	Trans women, any HIV status	US	Sevelius (PI)[22]
Individual-level: Peer Navigation	Feasibility & acceptability	Trans women, living with HIV, Trans women on PrEP	Brazil, US	Lippman(PI)[61], Sevelius PI)[62,63], Veras, Saggese
	Efficacy	Adults living with HIV, MSM living with HIV	South Africa	Lippman (PI)[23,64]
HIV prevention strategies				
HIV self-testing	Feasibility & acceptability	MSM, trans women	Brazil, US	Lippman (PI)[13-15,18], Sevelius
	Efficacy	MSM, Young women	South Africa, US	Lippman[16,17,65]
PrEP	Feasibility & acceptability	Trans women	US	Sevelius[19,20]
	Efficacy	Trans women	US, Brazil	Sevelius[21]

Group-level, peer-led intervention for trans women and the adaptation for Brazil (Sheroes). Sheroes addresses intersectional stigma through gender affirmation, empowerment, gender pride, and understanding gender-based power inequalities to build healthcare-seeking skills supported by a sense of self-worth[66]. In a pilot RCT with 77 trans women in the US, at 6-month follow up, HIV-negative and unknown status participants reported significant reductions in condomless intercourse and improved social support compared to control[22] (Table 1). Encouraged by findings, we conducted a systematic translation and adaptation for trans women in Brazil. After translating materials from English to Portuguese, we collected and integrated input from stakeholders (potential participants, collaborating agency staff) into an adapted draft intervention. We then conducted a feasibility and acceptability pilot with Brazilian trans women, iterating and adapting suggested changes. Sheroes was highly feasible and acceptable. Of 5 sessions, 75% participated in at least 4 sessions, and 87.5% participated in at least 3 sessions. Participants requested additional sessions, with feedback including: “To be able to talk openly about sex, without being judged, was amazing!"; "I was thinking of injecting industrial silicone, but after hearing others' experiences, I'm leaving this room with certainty I will not do that"; "It was great to find out how wide the world of trans women is, even those who are HIV+". In the anonymous feedback survey, all participants endorsed high satisfaction and would recommend the program to a friend. The efficacious Sheroes program, feasible and acceptable in Brazil, provides the basis for *Guerreiras.*

Individual-level peer navigation for trans women in Brazil (*Trans Amigas*). Following formative research with trans women and local stakeholders, who advocated for peer-based support programs to improve uptake of both HIV prevention and treatment[2], we designed the Trans Amigas project.[61] Trans Amigas is an adaptation of an efficacious peer navigation intervention developed by Dr. Lippman in South Africa, known as I-Care[67], integrating principles from social-cognitive theory[68] with the gender affirmation theory to meet the care and treatment needs of trans women in Brazil (Table 1). The intervention pairs participants with a peer navigator (PN) who is also a trans woman living with HIV to build trust based on shared experience. Trust then provides the foundation for the navigator and participant to work together to implement behavior change goals that facilitate engagement in care[69]. Among the most important social support mechanisms navigators play is aiding

in addressing stigma as a barrier to remaining in care[69]. While final results of the Trans Amigas PN intervention in Brazil are pending, to date participants and navigators alike have reported high levels of acceptability and the ongoing program is highly feasible: with 92% of eligible trans women approached accepting enrollment, 84% of the cohort retained, and 70% of trans women randomized to PN in consistent (monthly) contact with their navigator. Similar interventions have been successful among trans women in the US,[70] and, notably, in the I-Care trial, PN clients linked to care 1.60 times faster (95% CI: 1.29-1.99) and had nearly double the odds of being retained in HIV care (OR 1.83, CI: 1.01-3.33) than those in the control arm.[23]

HIV self-testing among trans women. We have extensive experience introducing HIV self-testing (HIVST) for populations who may experience HIV stigma-related barriers to accessing clinic-based testing, including conducting the first U.S. study among trans women[13] and early HIVST research with MSM in Brazil[14,15,18]; all demonstrating high levels of acceptability. Further, Dr. Lippman's research has established that access to HIVST improves HIV testing frequency among at-risk populations[17,65] and that peer-based distribution of HIVST is an efficacious, safe, and acceptable approach for disseminating test kits[17,16,65]. (Table 1) Following the 2017 release of the WHO *Guidelines on HIV Self-Testing and Partner Notification*[71], the Brazil approved the first HIV self-test for sale in pharmacies. In 2018 the government announced availability of HIVST through SUS, aiming to increase testing uptake for those less likely to access testing or who test less frequently than recommended, including transgender women[72]. The locally manufactured DPP HIV 1/2 Rapid Assay can use blood or oral fluid samples and has been successfully utilized by key populations in Brazil[73]. Important to this application, HIVST has been found to be a feasible and acceptable method of increasing PrEP persistence among sex workers by eliminating stigma-related barriers to routine HIV testing required during PrEP use[74].

Identifying and addressing barriers to PrEP uptake and persistence among trans women. MPI Sevelius has extensive research experience related to PrEP and trans women and has authored numerous publications describing barriers and facilitators to PrEP uptake among trans women, including PrEP stigma, anticipated and enacted experiences of stigma from healthcare providers, and concerns about adverse interactions between antiretrovirals and hormones[19-21,75]. She is currently leading the first trans-specific PrEP demonstration project to identify best practices in PrEP provision to increase uptake, adherence, and persistence among trans people, which includes the provision of peer navigation and addressing PrEP stigma. One community-based clinic partner, La Clinica de la Raza, focuses on serving trans Latina women who have had little to no access to healthcare and identifying barriers to PrEP uptake among monolingual Spanish-speaking Latina trans women. Dr. Sevelius is also co-leading an exploratory study using social marketing strategies to develop trans-specific PrEP messaging to address PrEP uptake barriers among trans women (R21MH110340).

Our team is uniquely poised to conduct this research, with expertise in HIV prevention research with trans women in Brazil and a history of successful collaboration. We underscore that combined local acceptability and feasibility data and global efficacy data warrants a trial. Further incremental feasibility research to combine approaches already proven feasible in the target population (i.e. an R34) would delay urgent interventions for trans women for whom few proven interventions to address stigma and improve HIV outcomes exist.

3.2 Innovation

1) *MULTI-LEVEL INTERSECTIONAL STIGMA INTERVENTION:* ***Guerreiras*** **is the first multi-level, multi-component 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, we are uniquely poised to develop the first evidence-based approach to improving the HIV prevention continuum among trans women through the lens of intersectional stigma.

2) *TRANS-SPECIFIC CONCEPTUAL MODEL AND INTERVENTION APPROACHES:* **Our conceptual framework for the intervention, gender affirmation theory, developed by MPI Dr. Sevelius, 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 emphasize that trans women experience a unique social context and intersectional stigma impacts that cannot be accounted for by interventions that were developed for MSM[19,76,77]. Our intervention approaches represent decades of trans-specific research and intervention development and testing.

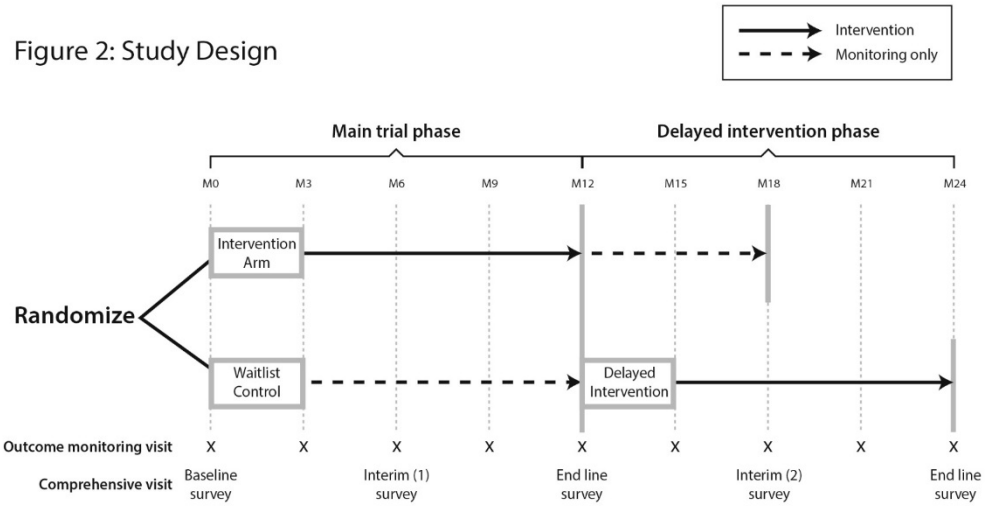
3) *STUDY OF MECHANISMS.* **Our study design, measurement, and analytic approach reflects the concept of intersectionality as more than an additive process of multiple stigmatized identities,**

recognizing 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- and social position-based stigma as well as stigma-related barriers to prevention, which, to our knowledge, has not been done previously. 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 proposal can contribute 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.

3.3. Research Approach

3.3.a Research Design Overview. We will conduct a randomized controlled trial, where upon enrollment participants will be randomized to either the *Guerreiras* intervention or to a wait-list control condition, in which participants will also receive the *Guerreiras* intervention after a one-year waiting period. We chose a wait-list control to safeguard ethical treatment of participants by ensuring that a potentially impactful intervention will be available to all after a brief waiting period. Rolling enrollment of 400 participants will take place over one year, with the intervention initiating activities as participants are assigned to a *Guerreiras* group (8-10 participants); group assignment will occur as soon as sufficient participants are enrolled. *Guerreiras* includes five group sessions over the course of 6-8 weeks, led by two peer navigators (PNs). Following group sessions, PNs will provide six months of peer navigation to each participant to support HIV testing (clinic or HIVST), PrEP uptake and persistence, harm reduction and other behavioral prevention as indicated, or HIV care (if participant tests positive). Groups will reconvene for a reunion session 3 months into navigation services (see Intervention Design 3.4). Follow-up data collection for the main trial phase will be conducted every three months, with comprehensive interviewer-administered surveys conducted at enrollment (baseline), 6 months (interim survey), and 12 months (endline), with brief monitoring surveys at the 3-month visits (e.g. 3- and 9-months) to assess prevention uptake (HIV testing, PrEP use, etc; see Figure 2, Study Design). This results in four post-enrollment follow-up visits per participant to document regular prevention uptake and two visits to document changes in stigma measures during the main trial phase. Qualitative interviews will be conducted with 18 participants at two timepoints (36 interviews total) to provide context to our exploration of intersectional stigma and gender affirmation, including how intersectional stigma impacts engagement with *Guerreiras* and HIV prevention uptake, how gender affirming programming impacts intersectional stigma, and insight into psychosocial mechanisms of change over time.

Figure 2: Study Design



The second phase of the study, the delayed intervention phase, provides an opportunity for the control arm to receive the *Guerreiras* intervention and simultaneously to a) follow intervention arm participants for a further six months to assess the persistence of intervention effects, and b) replicate main trial findings utilizing wait-list control data. Wait-list control participants will be assigned to a *Guerreiras* group for initiation of the full intervention following the main trial and completion of their endline survey. HIV testing will be monitored through clinical records at partnering services, through PN forms on HIVST distribution, and through monitoring visits every 3 months. PrEP initiation and persistence will be monitored using the national medications dispensing system (SICLOM), which is utilized in all public clinics. Dried blood spots (DBS) testing will assess drug levels among those on PrEP to measure of adherence and collected at clinic visits for PrEP dispensation. Comprehensive surveys measuring stigma domains will occur at 6-month intervals (see Measures 3.7).

3.3.b Study Setting and Population

Study setting. The proposed study will take place 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 LGBTI

communities, and both a global leader in equity of HIV treatment and a world center for gender transition care. The Brazilian investigative team has run a number of large state-funded surveys of the local transgender population, and has established the NIH-funded Trans*National Cohort (R01MD010678), an open cohort of trans women recruited through respondent driven sampling (RDS)[78]. Dr. Veras (site PI) has established relationships with a broad network of stakeholders, including public health and social services most frequented by the trans community and with the State HIV care reference and training center (CRT). The CRT includes a large outpatient clinic for HIV/AIDS (4000 patients currently in care), a small hospital, day-clinic, laboratory, HIV counseling and testing (HCT), a sexually transmitted infection (STI) clinic, and a prevention and research unit. CRT is also in charge of the HIV surveillance system for the state of São Paulo. Importantly, CRT is home to the largest and more comprehensive outpatient clinic for transgender health in the country and is the clinical research site for the Trans*National cohort and the Trans Amigas study (R34MH112177) of peer navigation for HIV-positive trans women. Procedures and activities for the proposal study will occur at the CRT and at SAE Campos Elíseos, which is the public health facility in central São Paulo catering to a large trans population. HIV testing, care and treatment, and PrEP are available at both clinic locations; participants who seroconvert will also be referred to one of these facilities for treatment. (see Letters of Support from State and Municipal Secretaries of Health and Trans*National). Finally, to ensure that participants who prefer not to engage with those specific clinic facilities also can participate, activities will also occur at the NUDHES community research office in central São Paulo. The easily accessible NUDHES space is home to a variety of NGOs and CBOs working with vulnerable populations (LGBT+, migrants, black communities) on social inclusion programming.

Study population. The target population is adult trans women in the São Paulo metropolitan area. Despite Brazil's progressive laws supporting LGBTI populations, including constitutional sanctioning of same-sex marriage, the right to change one's legal name according to gender identity, and the codified universal right to healthcare, research in Brazil has confirmed trans women's extreme vulnerability to violence, substance use, stigma and discrimination[79], with limited access to public health and social services[80,81]. Many trans women in Brazil also engage in sex work, in part as a result of the difficulty in finding other work due to stigma and high levels of social vulnerability in terms of education and socio-economic status[31,81-84]. Recent findings from Projeto Muriel, a large survey of trans populations in São Paulo by Dr. Veras, indicate that 86.8% of trans women have experienced discrimination for being trans women, particularly from family (70.1%), in employment (63.9%), by police (57.7%), and by health providers (47.4%). We aim to enroll a broad cross-section of trans women who mirror the demographics of the metropolitan area of São Paulo, approximately half of whom we will recruit from the Trans*National cohort and half from clinical services and outreach events.

3.4. Intervention Design.

3.4.a Overview. *Guerreiras* is a multi-level (group- and individual-level) intervention to improve engagement in the HIV prevention continuum among trans women in Brazil by addressing intersectional stigma, specifically identity-based stigmas related to gender identity and race, stigmas based on social position, e.g. engagement in sex work and substance use, and stigma-related barriers, specifically HIV and PrEP stigma. The group-level component of *Guerreiras* is facilitated by two peer navigators (PNs) and consists of 5 sessions conducted over 6-8 weeks. To address HIV stigma, one PN will be living with HIV and the other will be HIV-negative. Group content (see Table 2) is informed by gender affirmation theory and designed to address intersectional stigma through building gender pride (reducing internalized stigma), role modeling (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 *Guerreiras* consists of 6 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 six months of peer navigation re-affirm strategies learned during group sessions in one-on-one navigation sessions, with a reunion group session 3 months into navigation, which provides an opportunity to share experiences collectively.

Table 2. *Guerreiras* 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 internalized 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 health care (i.e. 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 (e.g., 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 (e.g. 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 is 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 internalization of intersectional stigma
Reunion (3 mos 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 health care providers to challenge structural and interpersonal enacted and anticipated stigma Reinforce gender pride to resist internalization of intersectional stigma
Navigation (for 6 mos post-groups)	Staying Connected / *Permanecendo Ligada*	Provide one-on-one individualized support for navigating current healthcare system, reinforcing concepts from group work, including problem-solving and strategies for coping with anticipated and enacted stigma

3.4.b. HIV self-testing and/or navigation to clinic-based testing. HIV self-testing (HIVST) will be introduced and demonstrated in session 1 and will be made consistently available to all *Guerreiras* participants for free through our public sector partnerships. HIVST is available in Brazil in the public sector[85]. PNs will bring HIVST kits to each session; *Guerreiras* participants will have the option of utilizing HIVST in groups, with their PN, or on their own. At each group session participants will be invited to debrief their HIVST experience with the group if they so choose. PNs will offer one-on-one support for HIVST before and after each group session as needed and will offer navigation to clinic-based HIV testing to those who prefer clinic-based testing. PNs will be trained in test counseling to ensure they are prepared to debrief test results, though very few social harms have been reported in HIVST studies with vulnerable populations[71,86,87]. PNs will record HIVST distribution and tests conducted with them or in the group on standardized case report forms (see section 3.6.e).

3.4.c. PrEP uptake, persistence, and adherence support. The most important indication for PrEP use is an expressed desire to use PrEP[88]. PNs will provide PrEP education and navigate participants to obtain PrEP upon request. PrEP uptake, persistence, and adherence support focus on empowering personal choice, self-assessment of HIV risk, desire for feeling safe during sex, and daily habit formation. Group sessions include a trans-specific personal HIV risk assessment and PrEP decision-making tool developed specifically for trans women. PrEP-related group session content focuses on documented key facilitators of persistence and adherence, including: 1) daily habit formation; 2) knowledge that PrEP is highly effective when used; 3) disclosure of PrEP use to housemates who may discover the medication; 4) making plans for travel and substance use; 5) information about safety, including lack of known PrEP drug interactions with feminizing hormones[21]; 6) clear information that PrEP can be taken with or without food, at any hour, and with alcohol; and 7) information about the flexibility of the regimen including that forgotten tablets should be taken when remembered (even if late), that a tablet should be taken if one is not sure that the scheduled tablet was taken, and that PrEP is highly protective even if occasional doses are missed (i.e. don't panic if you miss a dose)[19,89].

3.4.d. Ensuring a tailored prevention plan. While supporting PrEP uptake and persistence is urgent for trans women as a key population at high risk for HIV, PrEP will not be indicated for a small subset (~5-10%) who have clinical contraindications and/or low risk. Integral to *Guerreiras* intervention content and with support from PNs, participants will learn to accurately self-assess their HIV risk, options for accessing HIV prevention tools and support, and will adopt a prevention strategy tailored to their specific needs and preferences, e.g. HIV testing (clinic- or self-testing), PrEP, and/or behavioral risk reduction, such harm reduction or condom use.

3.4.e. Peer navigator training: Our team of investigators is experienced in staffing, training, and supervising clinical and behavioral intervention trials. We will identify and intensively train twenty potential peer navigators (PNs). Among these, 16 will be selected based on fit for facilitating the intervention. All PNs will be trans women, half will be living with HIV and currently receiving HIV care, and half will be HIV-negative and utilizing HIV prevention tools. PNs will be paired to ensure mixed status navigation teams to provide role modeling for HIV prevention and treatment, as well as to address HIV-related stigma for those who seroconvert or avoid testing due to fear of a positive result. PNs will be identified through stakeholders, clinics, and CBO partners as well as through NUDHES, a successful approach for identifying PNs for the Trans Amigas project.

The multi-week PN training will adapt detailed manuals we developed for facilitating the Sheroes group sessions and conducting peer navigation in Trans Amigas. For the group-level component, PNs will acquire skills in group facilitation through coaching, role plays, and mock sessions. HIV-related training content will include personalized HIV risk assessment, HIV test counseling (including HIV self-testing), PrEP, and HIV treatment. Stigma-related training content will include 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 (e.g. coping with anticipated and enacted stigma) and empowerment. For the individual-level component, PNs will be trained on the role of a PN, proving support to participants in developing a personalized HIV prevention plan, fostering an alliance, and ethical behavior, including maintaining appropriate personal/professional boundaries. PNs will learn about interactions they will have with participants (e.g., in-person meetings, phone calls, text messages) and how to record them (see 3.6e for intervention monitoring), assessing participant needs, and strategies for addressing routine and more challenging barriers to prevention and care. To learn about potential resources for participants, PNs will tour trans-friendly service agencies in São Paulo, including the LGBT Citizenship Center, the Alcohol and Drugs Psychosocial Care Center, NGOs providing harm reduction support, the Racial and Intolerance Crimes Police Station, and the Social Assistance Reference Center. PNs will meet with the study coordinator weekly to conduct case conferences, receive support, and problem-solve. The study coordinator will have biweekly calls with investigators to discuss issues and strategize solutions. Refresher trainings will be conducted regularly to improve facilitation and navigation skills, to train new PNs if staff turnover occurs, and to address challenges.

3.5. Participant Eligibility, Recruitment, Randomization, Retention.

3.5.a. Eligibility: Participants must be 18 years or older; assigned 'male' at birth but currently identify as female, transgender, transsexual, or *travesti* (a common term for trans women in Brazil); not be known to be HIV positive; be a resident of the São Paulo 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 will be placed on the degree to which the participant has transitioned legally or physically. Participants may be PrEP-naïve or have initiated PrEP; being on PrEP is not an exclusion criterion. While we do not anticipate encountering many trans women already taking PrEP, preliminary data indicate that a large proportion of trans women who initiate PrEP will struggle with persistence and require renewed engagement[19]. Based on current data, we expect a maximum of 5% to have initiated PrEP prior to enrollment. We will not require HIV testing to enter the study; any participant who enrolls and either discovers she is positive or seroconverts will remain enrolled with navigation focused on HIV treatment. Recruitment staff will use a brief screening tool to establish eligibility prior to enrollment.

3.5.b. Recruitment: Participants will be recruited from three sources over the course of 6 months: (1) those currently enrolled in the Trans*National Cohort in São Paulo; (2) trans women presenting for services at partnering clinics or presenting for HIV testing through the clinic run community-based programs; and (3) trans women recruited through targeted recruitment events. The Trans*National Cohort Study utilizes respondent-driven sampling (RDS) and has enrolled 565 HIV-negative women. Any participants not known to have seroconverted in the cohort will be invited to participate in *Guerreiras*. We expect to recruit approximately half of the participants through this method. We will also invite trans women testing negative for HIV at either SAE Campos Elíseos, the CRT, or through the community-based testing programs run by CRT to participate. The community-based testing program, called "Fique Sabendo" or "be in the know" is a state-run operation that visits areas where trans women work and congregate for testing. Finally, we will conduct recruitment events, advertised through trans-friendly locations, the PN team, and through social media, to ensure we reach trans women not seeking services or already in Trans*National. We aim to enroll half of the study participants through clinic partners and outreach events. (for details see Form E, Recruitment and Retention).

When a potential participant is interested in the study, staff will screen and enroll them, provide an appointment for screening and enrollment, or record preferred contact information to schedule an appointment. All participants will provide informed consent for study procedures, including clinical record extraction and PrEP eligibility exams (e.g. HIV and creatinine) if interested in PrEP, per national guidelines (see Human Subjects).

3.5.c. Randomization: Participants will be randomly assigned 1:1 to one of two arms using a computer generated "random order of assignment" list such that 200 will be assigned to the intervention arm and 200 will be assigned to the wait-list control arm. The random assignments will be placed in advance in sealed, numbered envelopes in each study location. To avoid potential bias based on timing or location of enrollment, we will use "block randomization," with randomly-permuted block sizes to avoid identification of the allocation

of the last participant in a block. For participants allocated to intervention, assignment to a *Guerreiras* group will occur as soon as there is sufficient enrollment to form a group.

3.5.d. Retention: Upon enrollment, participants will be asked to provide contact information, including address, cell phone/WhatsApp number, other social media contacts, and also to volunteer up to three individuals who can contact them should study staff be unable to do so. At each 3-month monitoring visit, staff will validate contact information in addition to completing data collection (see section 3.6.a & 3.6.b). The Brazilian study team has experience with these contact methods in retaining Trans*National and Trans Amigas study participants. (See Form E, Recruitment and Retention for further details on retention plans). Given the mobility and often unstable housing trans women experience, we expect to retain 75% of the cohort. To date just over 50% of Trans*National participants (an observational study) and just over 80% of Trans Amigas participants (an intervention study with consistent contact) have been retained; as a result, we believe retention will be closer to Trans Amigas retention rates. We account for attrition in the statistical power (see section 3.8).

3.6. Data Collection

3.6.a Monitoring Visits and Surveys: The data collection schedule includes visits every 3 months: every other visit (every 6-months) will include a comprehensive survey (see Figure 2); all surveys are interviewer-administered on encrypted study tablets. At enrollment, participants will provide informed consent and then respond to the first (baseline) comprehensive survey. Participants will complete two additional comprehensive surveys (interim and endline) during the main trial phase. During the delayed intervention phase all participants will respond to an additional interim survey and wait-list control participants will also respond to a final (endline) survey at the end of the period. Comprehensive surveys will assess hypothesized covariates and mediators of our primary and secondary outcomes (see Table 3). Brief monitoring surveys (15 minute) to record outcomes at 3-month intervals will capture: self-reported HIV risk behaviors and risk reduction practices (condom use or partner reduction); HIV testing; PrEP use (including refills and adherence); other prevention services sought and utilized (STI testing and treatment, harm reduction). The endline survey will include questions about engagement in study activities and interactions with navigators. We utilize measures that have been validated in Brazil when possible, including those we have used in prior studies and those we are currently validating in Trans Amigas (see Measures section 3.7 for more detail). Participants will be reimbursed for all study visits.

Participants may choose to schedule visits at any of the three project sites, to optimize convenience. For those on PrEP, data collection visits will be scheduled at the participant's clinic to ensure that PrEP distribution, HIV testing, DBS collection, and survey data collection is integrated efficiently into clinical care. Study staff will be available at each site. For participants with difficulty presenting at a study location, staff will offer interviews by phone or WhatsApp, to minimize missing data, though all attempts will be made to maximize in-person data collection. Interviewers will be trained on interviewing techniques, standard operating procedures, and human subjects research, including ensuring complete confidentiality. (See Form E, Human Subjects for details).

3.6.b PrEP Data Extraction: Data regarding PrEP use, which became available nationally for at-risk populations in December 2017, will be extracted from the national SICLOM (Sistema de Controle Logístico de Medicamentos) database, which captures all ARV distribution nationally. PrEP dispensing will be extracted quarterly from SICLOM and stored securely, including visit dates, pill count and dose, and any associated observations. We will utilize clinical records at the facilities to note visits for other purposes, including visits related to PrEP side effects (see 3.6.c below). The investigators have successfully utilized SICLOM for extraction of medication dispensing information in the Trans Amigas project.

3.6.c Clinic data extraction: Clinic-based HIV testing data and uptake of clinic-based prevention services, including STI testing and treatment, sexual health counseling, and HIV care visits (for those who seroconvert) will be extracted bi-annually, including visit purpose, dates, services received, HIV test result, and associated observations. Data from participant clinical files will be extracted electronically and uploaded to a secure data base kept by the study data managers (see Form E Human Subjects for details). Our team has successfully and safely extracted clinical data for Trans Amigas participants at the CRT and will utilize similar protocols.

3.6.d Drug Concentration Testing: Drug concentrations in the blood have emerged as strong correlates of protection in PrEP trials, accounting for the majority of the variation in PrEP benefits. Dried blood spots (DBS) are easy to collect, require no processing in the field, are easy to store and ship, and are feasible for monitoring drug concentrations among trans women in our current PrEP demonstration project. The DBS will be collected at the clinical sites at each visit for PrEP dispensation by trained staff and processed in accordance with procedures developed for previous studies. (Investigators have all utilized DBS for drug concentrations in previous studies). Staff will 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 dessicant packet and humidity indicator. DBS will be temporarily stored at each clinic in a freezer at -4C, then batch shipped monthly to the local laboratory for storage at -20C and batch tested quarterly using a validated method for quantification of drug concentrations of tenofovir and emtricitabine[90]. Adherence will be defined as having drug concentrations at levels required for protection (≥4 pills per week)[91].

3.6.e Intervention Monitoring. We will monitor intervention quality and fidelity using strategies from Trans Amigas, including a group session form (GSF) and a peer contact form (PCF). GCFs will record attendance using participant ID, date, and content and activities completed in each group session, and note distribution of HIVST to each participant in each session. PCFs are designed to track PNs' protocol-guided interactions with participants, noting each successful or attempted in-person navigation meeting, phone call, or text message. On PCFs, PNs note the date of contact, participant IDs, the topics discussed, and any required follow-up. Forms are entered into a database to monitor group session fidelity and track navigation contact over time. Each PN will meet weekly with the study coordinator to debrief intervention content and interactions with participants and to submit completed forms. The study coordinator will participate on weekly calls with the investigators to discuss client challenges or PN performance problems, re-training needs, and any modification or adaptation required to improve study processes. Investigators will review monitoring data on monthly calls.

3.6.f Qualitative interviews. We will conduct semi-structured in-depth qualitative interviews (IDIs) with 18 intervention participants at two time points (36 total IDIs). We aim to conduct one interview at the beginning of group sessions and one at the conclusion of peer navigation. PNs will identify participants who are early adopters or decliners of HIVST and/or PrEP (uptake or decline within the first two to three group sessions) and refer them for qualitative interviewing. If the participant is interested, the PN will describe the interview procedures and schedule an appointment. Qualitative interviews will be conducted in-person by a trained interviewer, supervised by co-I Saggese. Interviews will last approximately 1 hour, will be audio recorded, and will explore uptake/declination of and persistence with prevention tools in the context of the conceptual framework using probes specifically related to the intersectional stigma domains of interest: internalized, anticipated, and enacted stigma related to gender identity, race, HIV, PrEP, and other stigmas associated with marginalized social positions and behaviors (e.g. sex work, drug use), as well as stigma resilience. The structured interview guide will allow for organic exploration of additional emergent stigma domains, as appropriate, and explore how participants perceive intersections in identity-based stigma, social position-based stigma, and stigma related barriers to prevention and the impact of the intervention on stigma resilience.

3.7 Measures

Primary Exposure: Randomization arm – intervention or wait-list control – will be considered the primary predictor variable for all primary analyses and recorded on study enrollment forms. Because the degree of engagement with the intervention will vary by individual, we will also capture intervention dose on study monitoring forms as a secondary exposure measure for additional (per protocol) analyses.

Primary Outcomes: (Evaluation: Aims 1 & 2): HIV testing uptake will be 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 utilized for sample size calculations. We will document *PrEP initiation*, defined as a participant filling their first PrEP prescription, through PrEP dispensing information in the national SICLOM database. However, because initiation does not imply continued use, we will 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, STI care) are listed in Table 3, below.

Mediators: Intersectional Stigma: We will include a comprehensive suite of stigma measures that will be examined together in mediation and moderation analyses (see Analysis section 3.8). To explore the concept of intersectional stigma, we will analyze potential interactions between the stigma domains. This reflects the concept of intersectionality as more than an additive process of multiple stigmatized 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 will include quantitative measures of internalized, 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 operationalized as coping self-efficacy and healthcare empowerment in the context of anticipated

and enacted stigma. Comprehensive surveys will be conducted at enrollment, interim, and endline at 6-month intervals; we do not expect changes in stigma every 3 months (interval for outcomes monitoring).

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

Table 3: Primary and Secondary Measures

Domain	Instrument/measure	Data source	Frequency of data collection/extraction
PRIMARY EXPOSURE			
Intervention	Randomization arm	Enrollment/study records	Continuous during enrollment
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 bi-annually, Continuous, Monitoring visits (3-monthly)
PrEP initiation	Binary: Initiation of PrEP in past 3-months*	National data (SICLOM)	Extract quarterly
PrEP persistence	Binary: PrEP dispensed with 80 or more days covered in 3-months per dispensation records*	National data (SICLOM)	Extract 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 bi-annually, Monitoring visits (3-monthly)
	Condom use (consistent use with regular and occasional partners and clients)	Clinical data extraction; Self-report	Extracted bi-annually, 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	*Internalized*, *anticipated*, and *enacted* stigma related to: Identity-based stigma: gender[92], race[93] Social position-based stigma: sex work[94], substance use Stigma-related barriers: HIV stigma[95]; PrEP stigma [96]	Self-report - Surveys	Comprehensive visits (6-monthly)
	Stigma resilience: Coping self-efficacy [97-99] Healthcare empowerment[100]	Self-report - Surveys	Comprehensive visits (6-monthly)
Gender affirmation	Need for and experiences of gender affirmation[12] Transgender group identity[92]	Self-report - Surveys	Comprehensive visits (6-monthly)
Social, structural barriers to / facilitators of prevention	Depression [101-103], substance use[104], social support[105,106], social cohesion[107,108], relationship violence[109], trauma[110], access to clinical care and services received, food insecurity[111,112].	Self-report - Surveys	Comprehensive visits (6-monthly)

*calculated among those with indications for PrEP use.

3.8 Data Analysis Plan and Statistical Procedures:

Preliminary analyses, missing data. Frequency tables for all variables and measures of central tendency and variability for continuous variables (e.g., stigma scores) will characterize the sample and will be stratified by randomization arm to check for imbalances. If arms differ significantly at baseline on one or more covariates, we will use causal modeling methods (e.g., propensity scores, targeted maximum likelihood estimation) to obtain the desired marginal effect estimates under the counterfactual assumption of balanced arms[113-117]. We will address incomplete data with multiple imputation (MI)[118]; MI makes the relatively mild assumption that incomplete data arise from a conditionally missing-at-random (MAR) mechanism[119]. Auxiliary variables will be included to help meet the MAR assumption[120,121] and sensitivity analyses will be conducted with weighted MI[122] to assess the robustness of the MAR assumption[123]. SAS[124] and M*plus*[125] will be used for analyses.

Primary analyses for Aims 1 and 2. We expect HIV prevention outcomes to improve in the intervention arm relative to the control arm during the main trial phase. We hypothesize that, following the intervention, odds of HIV testing will be higher for intervention participants relative to control participants (Aim 1, Hypothesis 1). We also hypothesize that, following the intervention, the odds of PrEP initiation and persistence will be higher for the intervention group than for the control group (Aim 2, Hypothesis 2). 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[126]. Moreover, within-subject outcome correlations are considered nuisance parameters rather than quantities of interest to be modeled explicitly. Accordingly, generalized estimating equations (GEE) will be used for the primary analyses to test Hypotheses 1 and 2 using time-averaged comparisons of post-baseline (follow-up) measurements of intervention group with control group in the main trial phase. Alpha (α) will be set at .05 for these two planned comparisons. The alternating logistic

regression (ALR) approach implemented in SAS PROC GENMOD will be used to address the 3-level clustering of observations within participants and participants assigned to *Guerreiras* group leaders. This analysis will follow an intent-to-treat (ITT) approach by including all randomized participants. Further detail on the analytic model and secondary analyses, including secondary outcomes, intervention persistence, and intervention replicability, are included in Form E, Statistical Design and Power.

Primary Analyses for Aim 3. GEE will be used to test Aim 3 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 internalized stigma. Analyses will follow the same ITT modeling approach as described above for Aims 1 and 2, except that a normal distribution and identity link will be employed to analyze continuous, normally-distributed stigma scores. These hypotheses will be tested via planned time-averaged comparisons of post-baseline measurements of the two arms in the main trial phase. These comparisons will be tested at α=.05 per comparison.

We will also explore whether stigma measures at interim (six-months) surveys mediate the relationship between intervention assignment and subsequent outcomes as well as whether combinations of stigmas measures at baseline and six-months act synergistically (interact) and moderate the exposure-outcome associations in order to assess intersectional stigma. We will also assess whether measures of gender affirmation and transgender group identity increase over the course of the intervention and mediate the relationship between intervention arm and subsequent outcomes. Further detail on Aim 3 secondary analyses, including mediation and moderation, are in Form E, Statistical Design and Power.

Statistical power. We computed minimum detectable effect sizes for primary outcomes using the two-group repeated proportions module in NCSS PASS 16[127]. The study will begin with 400 participants equally allocated to two study groups. Assuming 25% attrition, data from 300 participants will be available for analysis at all time points. We further lowered the effective sample size (ESS) to account for correlations between participants receiving the intervention from the same *Guerreiras* PN pairs, using a range of plausible intraclass correlations (ICC)s within PN pairs. Assuming α=.05 and power=.80, with four post-baseline measurements and assuming control group proportions P_0=.50 for HIV testing and P_0=.05 for PrEP use, we will have sufficient power to detect small to medium effects. This includes effects as low as 13% and 8% difference in proportion in HIV testing and persistent PrEP use, respectively, in the intervention arm compared to control. Effect size estimates for primary analyses (all Aims 1, 2, and 3) fall between cutoffs of .20 and .50 for small and medium standardized effect sizes[128]. Statistical power is fully elaborated in Form E, Statistical Design and Power.

Qualitative data analysis: We will optimize the longitudinal qualitative data we are collecting through best practices for analysis of this type of data, including tracking coding and analysis decisions over an extended analysis period, establishing clear coding and review processes, and using concept mapping to track codes, relationships between codes, and thematic groupings[129]. Audio-recordings will be transcribed; transcriptions will be managed using Atlas.ti, software designed to assist with textual datasets[130]. Functions include assisting with indexing, coding, searching, and mapping. Guided by gender affirmation theory and the lens of intersectional stigma, we will approach the qualitative analyses with the aim of elucidating how relationships of power or disadvantage based on stigma related to gender, race, social position (e.g. sex work, substance use), and stigma-related barriers (e.g. HIV and PrEP stigma) operate as mutually reinforcing rather than distinct systems of oppression, how these social and structural processes evolve over time and within the context of the intervention[131]. MPI Sevelius and Co-I Saggese will independently review the transcripts, beginning with analyzing cross-sectional baseline data separately and then grouping interviews by participant at endline to reflect temporality of experiences within each participant. Investigators will identify prospective codes with particular attention to interactions between and nesting within codes, highlighting intersections of identities and social processes over time. We will draft evolving summaries, including key insights and supporting data, and will convene weekly to discuss interpretations and arrive at consensus on key themes, navigating evolving interpretations over time through concept mapping with periodic coding review[129].

Conclusion. The proposed multi-level 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[9]. Agencies and community leaders are rightfully demanding efficacious interventions to curb the devastating impact of HIV on trans communities. This application balances this impassioned outcry for urgent action with the measured, scientific rigor 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.

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