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Instituto Nacional de Infectologia Evandro Chagas

Doutorado em Pesquisa Clínica em Doenças Infecciosas

Brenda Regina de Siqueira Hoagland

Conhecimento, interesse, decisão sobre o uso e adesão precoce à profilaxia pré-exposição (PrEP) entre homens que fazem sexo com homens (HSH) e mulheres transexuais (Trans) participantes no estudo PrEP Brasil

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Profª. Drª Valdiléa Gonçalves Veloso dos Santos

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Este trabalho é dedicado para todas aquelas pessoas que podem se beneficiar com o seu resultado.

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“Uma pessoa inteligente resolve um problema, um sábio o previne.”
Albert Einstein

Hoagland, B. Rio de Janeiro, 2016. **CONHECIMENTO, INTERESSE, DECISÃO SOBRE O USO E ADESÃO PRECOCE A PROFILAXIA PRÉ-EXPOSIÇÃO (PREP) ENTRE HOMENS QUE FAZEM SEXO COM HOMENS (HSH) E MULHERES TRANSEXUAIS (TRANS) PARTICIPANTES NO ESTUDO PREP BRASIL.** Tese [Doutorado em Pesquisa Clínica em Doenças Infecciosas] – Instituto Nacional de Infectologia Evandro Chagas

RESUMO

Introdução: A profilaxia pré-exposição (PrEP) utilizando a combinação de dois antirretrovirais, o disoproxil fumarato de tenofovir (TDF) e emtricitabina (FTC), por via oral tem se mostrado eficaz na prevenção do HIV em homens que fazem sexo com homens (HSH) com alto risco de aquisição da infecção. O Brasil apresenta a maior população da América Latina vivendo com HIV/AIDS e uma epidemia concentrada em HSH com uma prevalência de 14,2% quando comparado a população geral, que é de 0,6%. A população jovem de HSH são quase 40% dos casos de AIDS, com um aumento de 41,3% (entre 15-19 anos) e 25,1% (entre 20-24 anos) entre 2004 e 2013. Apesar da população de mulheres transexuais (Trans) representarem uma parcela menor que os HSH, elas apresentam índices extremamente elevados de risco e diagnóstico de infecção pelo HIV. Deste modo a epidemia de HIV persiste sem decréscimo entre HSH e Trans, com uma elevada proporção desses indivíduos desconhecendo sua condição sorológica. Neste contexto, foi desenhado o PrEP Brasil (NTC01989611), um estudo multicêntrico, aberto, de demonstração de PrEP para acessar a intenção de uso, viabilidade e segurança de oferecer PrEP no Sistema Único de Saúde (SUS) para a população de HSH e Trans de alto risco para o HIV. **Objetivo**: Descrever o conhecimento, o interesse e a decisão sobre o uso e a adesão precoce à PrEP entre HSH e Trans, através dos níveis de TDF/FTC medidas em amostras de sangue seco (DBS) coletadas na visita de semana 4 e seus fatores associados no estudo demostrativo PrEP Brasil. **Primeiro Artigo:** Descrever o conhecimento e interesse da PrEP entre HSH e TRANS participantes do PrEP Brasil. Conhecimento e interesse para usar PrEP assim como outros métodos de prevenção foram dados na forma de percentuais. Modelos de regressão logística foram usados para explorar e quantificar os fatores associados ao conhecimento e aceitabilidade de PrEP. Variáveis com $p < 0.1$ na análise bivariada foram incluídos nos modelos ajustados iniciais. O modelo ajustado final incluiu variáveis que persistiram significantes (no limite de 5% da significância) assim como as variáveis que foram consideradas de confusão (qualquer uma que modificasse o odds ratio estimado em mais que 10%). A prevalência do HIV foi calculada excluídos os casos faltantes (n=52 não realizou teste rápido do HIV). **Segundo Artigo**: Descrever a decisão de uso e a adesão precoce a PrEP entre HSH e mulheres transexuais através da medição dos níveis séricos de Tenofovir e Emtricitabina em amostras de sangue seco coletadas em papel de filtro (DBS) na semana 4 do estudo PrEP Brasil, assim como seus fatores associados. Também foram descritas as características demográficas e de risco da população incluída no estudo. Variáveis descrevendo as características dos indivíduos potencialmente elegíveis (incluídos e não incluídos), assim como por centro de estudo que o participante foi incluído foi apresentado em números absolutos e proporções. As distribuições foram comparadas usando análises de qui-quadrado e Kruskal-Wallis. A decisão de usar PrEP foi definida como o número de participantes incluídos dividido pelo número de participantes potencialmente elegíveis na pré-triagem menos aqueles

clinicamente inelegíveis (nas vistas de triagem e inclusão). Os preditores dos níveis de TDF/FTC foram acessados utilizando modelos de regressão logística ordinal. Apenas variáveis estatisticamente significantes a 5% no modelo não ajustado foram mantidas no modelo ajustado. Os resultados foram reportados como odds ratio, que podem ser interpretados como o efeito no odds sendo a categoria dos níveis de drogas mais altos versus os mais baixos. A associação de sintomas gastrointestinais e os níveis de drogas, medidos na visita de semana 4, foram também analisados usando modelos de regressão logística ordinal. Adicionalmente, para explorar possíveis efeitos do uso de hormônios nos níveis de TFV-DP em Trans, foram feitas duas abordagens de modelagens, ode foi usado: 1) modelo de regressão logística usando ≥4 doses/semana como resultado e uso/não-uso de hormônios como a variável dicotômica explanatória, 2) modelo de regressão logística linear com concentrações de TVF-DP como a variável contínua de resultado e uso/não-uso de hormônios como a variável dicotômica explanatória. As análises foram feitas usando o PROC GENMOD disponível no Software SAS e a suposição de odds proporcional foi verificada através do Teste de Pontuação. **Conclusões:** O estudo mostrou que a aceitabilidade e o interesse pela PrEP foi elevada entre HSH e mulheres transexuais e associada a comportamentos sexuais de alto risco para infecção pelo HIV, indicando que estes indivíduos estão interessados em novas estratégias de prevenção. Os resultados sugerem que a PrEP pode ser implementada com sucesso no Sistema Único de Saúde brasileiro para esta população específica. A elevada proporção de indivíduos com alcançaram níveis séricos protetores de TDF/FTC é encorajador e a alta adesão a PrEP sugere que esta pode ser uma estratégia eficaz na redução da infecção pelo HIV entre HSH e Trans em nosso meio.

Palavras-chave: 1.PrEP 2. Prevenção ao HIV 3.HSH. 4. Mulheres Transexuais e Travestis 5.Conhecimento 6.Aceitabilidade 7.Níveis de Droga 8.Adesão

Hoagland, B. Rio de Janeiro, 2016. **AWARENESS, WILLIGNESS, UPTAKE AND EARLY ADHERENCE AMONG MEN WHO HAVE SEX WITH MEN AND TRANSGENDER WOMEN PARTICIPANTS IN PREP BRASIL STUDY.**Tese [Doutorado em Pesquisa Clínica em Doenças Infecciosas] – Instituto de Pesquisa Clínica Evandro Chagas

ABSTRACT

Introduction: Antiretroviral pre-exposure prophylaxis (PrEP), with daily oral tenofovir disoproxil fumarate (TDF) in combination with emtricitabine (FTC),has been shown to be efficacious for HIV prevention for high-risk men who have sex with men (MSM). Brazil has the largest population of individuals living with HIV/AIDS in Latin America, and a concentrated epidemic with an estimated HIV prevalence of 0.6% in the general population and 14.2% prevalence among MSM. Young MSM account for nearly 40% of AIDS cases, with an increase of 41.3% (aged 15-19 years) and 25.1% (aged 20-24 years) observed in this group from 2004 to 2013. Although transgender women (Trans) represent a smaller population than MSM, they have extremely elevated HIV infection rates and very high risk for HIV infection. Thus, the HIV epidemic in Brazil persists unabated in MSM and Trans, with a high proportion of individuals remaining unaware of their HIV status**.** In this context, the PrEP Brasil Study (NCT01989611), a multicenter, open-label, PrEP demonstration project, was designed to assess uptake, safety and feasibility of PrEP provided for high risk MSM and Trans through the Brazilian public health system (*Sistema Único de Saúde*- SUS). **Objective**: Describe PrEP awareness, willingness, uptake, early adherence and its associated factors among MSM and Trans, as well as describe TDF/FTC drug levels measured in dried blood spots (DBS) at week 4 and its associated factors in the PrEP Brasil demonstration study. Also, we describe baseline demographic and risk characteristics of the study population. **First Article**: Describe PrEP awareness and willingness, also its associated factors among MSM and Trans participants from PrEP Brasil Study. Awareness and willingness to use PrEP as well as other HIV prevention measures are given as percentages. Logistic regression models were used to explore and quantify the association of factors with PrEP awareness and willingness. Variables with $p<0.1$ in bivariate analysis were included in the initial adjusted models. The final adjusted models included variables that remained significant (at 5% significance threshold) as well as variables that were considered confounders (i.e., those that changed the odds ratio estimate of any of the remaining variables by more than 10%). The prevalence of HIV was calculated excluding missing cases (HIV rapid test 'not performed', n=52). **Second Article**: Describe PrEP Uptake and Early Adherence among HSH and transgender women using TDF/FTC drug levels measured in dried blood spots (DBS) at week 4 and its associated factors, as well as describe baseline demographic and risk characteristics of the study population in the PrEP Brasil demonstration study. Variables describing the characteristics of potentially eligible individuals (enrolled and not enrolled), as well as enrolled participants by site location are presented in terms of absolute numbers and proportions distributions were compared using chi-square statistics or Kruskal-Wallis. PrEP uptake was defined as the number of participants enrolled divided by the number of potentially eligible at the pre-screening minus the clinical ineligible (at screening and enrollment visit. Predictors of drug levels were assessed using ordinal logistic regression models. Only variables statistically significant

at 5% in the unadjusted model were kept in the adjusted model. The results are reported in terms of odds ratio, which can be interpreted as the effect of the variable on the odds of being in a higher versus lower category of drug levels. The association of GI symptoms and drug levels, both measured at week 4 was also evaluated using ordinal logistic regression models. Additionally, to explore possible effects of hormone use on TFV-DP levels among Trans, two modeling approaches were used: 1) a logistic regression model with ≥4 doses/week as the outcome and use/non-use of hormone as the dichotomous explanatory variable, 2) a linear regression model with TFV-DP concentration as the continuous outcome variable and use/non-use of hormone as the dichotomous explanatory variable. Analyses were performed using PROC GENMOD available in the Software SAS and the assumption of proportional odds was checked using the Score test. **Conclusions**: The study showed that PrEP acceptability and willingness was high among MSM and transgender women and its association with riskier behavior is reassuring as it indicates that those individuals who are at higher risk of HIV infection are interested in this new prevention strategy. Our results show that PrEP for high risk MSM and trans women can be successfully delivered in the context of the Brazilian Public Health System. The high proportion of participants achieving protective drug levels is encouraging. Moreover, high PrEP early adherence suggests that PrEP use may be an effective strategy to reduce HIV infection among MSM in our setting

Keywords: 1.PrEP 2.HIV prevention 3.Men who have sex with men 4.Transgender women and travestites 5. Awareness 6.Willingness 7.Drugs levels 8.Adherence

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LISTA DE ABREVIATURAS

AIDS	Acquired Immunodeficiency Syndrome; Síndrome da Imunodeficiência Adquirida
ART/TAR	Antiretroviral Therapy / Terapia Antirretroviral
ARV	Antirretrovirais
PEP	Post-exposure prophylaxis/Profilaxia Pós-Exposição
PrEP	Pre-exposure prophylaxis/Profilaxia Pré-Exposição
CDC	US Centers for Disease Control
FDA	US Food and Drug Administration
TDF	Tenofovir
FTC	Emtricitabina
GI	Gastrintestinal; Trato Gastrointestinal
HBV	Vírus da Hepatite B
HCV	Vírus da Hepatite C
HIV	Human Immunodeficiency Virus; Vírus da Imunodeficiência Humana
IBGE	Instituto Brasileiro de Geografia e Estatística
IDU	Drug Injection User; Usuário de Drogas Injetáveis
MS	Ministério da Saúde do Brasil
MSM/HSH	Men who have sex with men; Homens que fazem sexo com homens
TRANS	Mulheres Transexuais/Travestis; Transexual Woman
PEP	Post-exposure prophylaxis; Profilaxia Pós-exposição
PrEP	Pre-exposure prophylaxis; Profilaxia Pré-exposição
WHO/OMS	World Health Organization - Organização Mundial de Saúde
ZDV/AZT	Zidovudina/Azitotimidina
FIOCRUZ	Fundação Oswaldo Cruz

USP	Universidade de São Paulo
CRT-SP	Centro de Referência e Treinamento em DST/AIDS de São Paulo
DBS	Died Blood Spot/Amostras de Sangue Seco
OR	Odds Ratio
DST/STD	Doenças Sexualmente Transmissíveis/ Sexually Transmitted Diseases

1 INTRODUÇÃO

Em 05 de junho de 1981, o Centro de Controle de Doenças (CDC) dos Estados Unidos publicou os cinco primeiros casos confirmados de pneumonia por *Pneumocytis Carinii* diagnosticados em cinco jovens, do sexo masculino, classificados como homossexuais(1). Três anos após a divulgação desses casos, os pesquisadores Luc Montagnier e Robert Gallo, isolaram pela primeira vez o vírus da imunodeficiência humana (HIV), causador da Síndrome de Imunodeficiência Adquirida (AIDS)(2,3). Apesar de ter se passado mais de 30 anos de epidemia de AIDS, com diversos avanços conquistados no âmbito do conhecimento da fisiopatogenia do HIV e o desenvolvimento da terapia antirretroviral altamente potente (HAART), o número de casos permanece inaceitavelmente elevado, com 21.3 milhões de casos de infecção pelo HIV no mundo, com em torno de 6.000 mil novas infecções por dia, onde países do continente africano colaboram com 1.5 milhões de casos/ano(4).

No ano de 1987, foi apresentado o primeiro medicamento antirretroviral, a Azitotimidina (AZT), considerado eficaz para o tratamento da AIDS(5). E, em 1994, foi publicada a eficácia do uso do AZT na redução da transmissão materno-infantil do HIV-1(6), abrindo caminho para que novos estudos, utilizando antirretrovirais na prevenção da infecção pelo HIV fossem desenvolvidos, levando a publicação de uma série de casos-controles, indicando a eficácia do uso desses medicamentos na prevenção do HIV em exposições ocupacionais(7).

A transmissão sexual do HIV depende de vários fatores, entre eles o tipo de prática sexual, o nível de carga viral do parceiro infectado e a presença de outras condições no parceiro saudável que favoreça a transmissão do vírus, como a presença de outras doenças sexualmente transmissíveis (DST). Relações sexuais anais insertivas

desprotegidas, com parceiros sabidamente soropositivos, apresentam um risco de transmissão do HIV que varia entre 0.1 a 3%, por exposição sexual(8).

Até o momento, o pilar para a prevenção do HIV tem se baseado no uso de preservativos nas relações sexuais. Segundo dados do Ministério da Saúde, 94% dos brasileiros tem conhecimento de que os preservativos são a maneira mais eficaz de prevenir o HIV e outras doenças sexualmente transmissíveis, no entanto apenas 45% da população sexualmente ativa usa o preservativo de forma consistente em todas as relações sexuais com parceiros casuais(6).

Seguindo o racional sobre o uso de antirretrovirais para a prevenção do HIV materno-infantil e ocupacional, estudos envolvendo o uso destes medicamentos como forma de profilaxia pré-exposição (PrEP) passaram a ser desenvolvidos. Avaliações pré-clínicas em primatas, utilizando os antirretrovirais Tenofovir Disoproxil Fumarato (TDF) e a Emtricitabina (FTC), mostraram que o uso isolado de qualquer um destes medicamentos teve efeito protetor em 70 a 100% dos casos e, o uso da associação TDF/FTC, teve efeito 100% protetor, mesmo após exposições retais repetidas ao HIV nesses primatas, sugerindo que a proteção é um reflexo da alta concentração desses medicamentos nos tecidos e fluídos genitais, da meia-vida intracelular longa e da atividade nos macrófagos(9–15).

Estudos envolvendo PrEP foram realizados em diversas populações mostrando eficácia variável entre homens que fazem sexo com homens (HSH), casais sorodiscordantes, homens e mulheres heterossexuais(16–19). Mas, em 16 de julho de 2012, o órgão americano que administra alimentos e medicamentos nos Estados Unidos da América (U S Food and Drug Administration – FDA), aprovou o uso da combinação de TDF/FTC, para a prevenção da infecção pelo HIV(20). Essa decisão foi baseada nos

resultados publicados do estudo iPrEx(16) que avaliou o uso oral e diário do TDF/FTC em 2499 homens que fazem sexo com homens (HSH) e mulheres transexuais (Trans) com elevado risco à infecção pelo HIV. Este estudo foi conduzido no Peru, Equador, África do Sul, Brasil, Tailândia e Estados Unidos e demonstrou que o uso diário do medicamento foi seguro e eficaz, podendo prevenir a infecção pelo HIV em 44%(21). Estudos posteriores, utilizando modelos matemáticos, analisaram os níveis de medicação entre os participantes do estudo, mostrando que o uso de 4 doses/semana ou 7 doses /semana de TDF/FTC poderiam predizer, respectivamente, uma eficácia de prevenção do HIV de 96% e 99%(22). Isso sugere que os níveis de adesão estão proporcionalmente relacionados ao nível de eficácia da PrEP.

Após a apresentação desses resultados, consensos para uso da PrEP foram publicados e a Organização Mundial de Saúde (OMS) recomendou que os países desenvolvessem projetos locais demonstrativos de implementação da PrEP para populações altamente vulneráveis à infecção pelo HIV(23,24). Desde então, novos estudos foram conduzidos, em especial para as populações de HSH e Trans com alto risco de aquisição do HIV. Um estudo demonstrativo americano de PrEP demonstrou que o uso da PrEP em uma coorte de HSH e mulheres transexuais reduziu extremamente a incidência de HIV nesta população, apesar da alta incidência de outras doenças sexualmente transmissíveis. Além disso, verificou-se que a adesão à PrEP foi mais alta entre àqueles que reportavam maior comportamento sexual de risco(25). O estudo PROUD conduzido no Reino Unido, com a mesma população, demonstrou que o uso diário de TDF/FTC conferiu níveis de proteção de 86% contra a infecção pelo HIV e não foi visto aumento na incidência de outras DST com o uso da PrEP(26). O estudo iPERGAY, conduzido na França e no Canadá, avaliou o uso do TDF/FTC conforme demanda. Os participantes fizeram uso do medicamento apenas em situações sexuais de

risco, com a orientação posológica de dois comprimidos 24h antes da relação sexual, seguido de um comprimido administrado 24h e 48h após a exposição, conferindo uma proteção de 86% contra a infecção pelo HIV(27).

O Brasil tem a maior população de indivíduos vivendo com HIV/AIDS na América Latina(28), com uma epidemia concentrada, onde a prevalência de HIV estimada na população geral é de 0.6% (0.4% em mulheres e 0.8% em homens) e de 14.2% em HSH(29). A população jovem de HSH colabora com em torno de 40% dos casos de AIDS, com um aumento de casos de 41.3% na faixa etária entre 15-19 anos e 25.1% entre 19-24 anos, observado neste grupo de 2004 a 2013(8). Apesar das mulheres transexuais representarem uma população menor que os HSH, estas apresentam elevados índices de infecção pelo HIV e elevado risco para aquisição do vírus(30,31). Os dados no Brasil são escassos sobre os níveis dessa infecção na população de mulheres transexuais, mas os relatos são de altas taxas de prevalência de HIV, impulsionado pela interação de diversos níveis de risco que contribuem para um processo dinâmico de aumento da vulnerabilidade ao HIV/AIDS neste grupo. Assim, a epidemia de HIV/AIDS no Brasil permanece sem redução entre HSH e Trans, com uma elevada proporção de indivíduos desconhecendo sua condição sorológica(29). Neste contexto, foi desenvolvido o PrEP Brasil (NCT01989611).

O PrEP Brasil é um estudo de 48 semanas, multicêntrico, longitudinal, prospectivo, aberto, demonstrativo de PrEP, que foi desenhado para acessar a decisão de uso, a adesão, a segurança e a viabilidade de oferecer PrEP para HSH e Trans de alto risco no Sistema Único de Saúde (SUS) brasileiro. O estudo ocorreu em três centros de prevenção e tratamento ao HIV, no Rio de Janeiro (RJ) e em São Paulo (SP), duas cidades brasileiras com altas taxas de infecção pelo vírus(32). Os centros de estudo participantes foram o Instituto Nacional de Infectologia Evandro Chagas da Fundação

Oswaldo Cruz (FIOCRUZ) no RJ, Universidade de São Paulo (USP) e Centro de Referência e Treinamento em DST e AIDS (CRT-SP), ambos em SP. Todos os centros de estudo têm ampla experiência na prevenção e no tratamento do HIV no contexto do SUS, assim como em pesquisa clínica.

1.1 OBJETIVOS

Objetivo Principal

Estudar na população HSH e Trans o conhecimento, o interesse, a decisão e adesão precoce ao uso da profilaxia pré-exposição ao HIV com uso oral e diário de tenofovir e emtricitabina em dose fixa combinada.

Objetivos Secundários

1. Determinar a proporção dos participantes do estudo que conhecem e dos que se interessam em usar PrEP e outras intervenções biomédicas de prevenção;
2. Determinar entre os participantes elegíveis para PrEP a proporção dos que decidem utilizar essa intervenção;
3. Descrever o perfil sociodemográfico e de comportamento sexual dos participantes do estudo;
4. Mensurar a adesão precoce a PrEP utilizando os níveis de droga e estudar seus fatores associados;
5. Descrever a prevalência de eventos gastrointestinais relacionados à PrEP (síndrome de início) na visita de semana 4 do estudo.
6. Descrever a prevalência de doenças sexualmente transmissíveis entre os participantes do estudo;
7. Descrever a prevalência de uso de álcool e drogas entre os participantes do estudo.

1.2 ESTRUTURA DA TESE

Os capítulos de revisão da literatura, metodologia, resultados e discussão foram apresentados na forma de dois artigos:

1-**Awareness and willingness to use Pre-Exposure Prophylaxis (PrEP) among men who have sex with men and transgender women in Brazil** (Conhecimento e Interesse para usar Profilaxia Pré-Exposição (PrEP) entre homens que fazem sexo com homens e mulheres transexuais no Brasil).

2- **High Pre-exposure Prophylaxis Uptake and Early Adherence among Men Who Have Sex with Men and Transgender Women at Risk for HIV Infection: The PrEP Brasil Demonstration Project** (Elevada Decisão de uso da Profilaxia Pré-Exposição e Adesão Precoce entre Homens que fazem sexo com Homens e Mulheres Transexuais em Risco para Infecção pelo HIV: O Projeto Demostrativo PrEP Brasil).

2 PRIMEIRO ARTIGO

Autores:

Brenda Hoagland[1], Raquel B. De Boni[1], Ronaldo I. Moreira[1], José Valdez Madruga[2], Esper G. Kallas[3], Silvia Pereira Goulart[2], Natalia Cerqueira[3], Thiago Torres[1], Paula M.Luz[1], Nilo Martinez Fernandes[1], Albert Y. Liu[4], Beatriz Grinsztejn[1] e Valdilea G. Veloso[1]

[1]Instituto Nacional de Infectologia Evandro Chagas, FIOCRUZ. Rio de Janeiro, Brazil

[2]Centro de Referência e Treinamento em DST/AIDS, São Paulo, Brazil

[3]Universidade de São Paulo, Brazil

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ORIGINAL PAPER

Awareness and Willingness to Use Pre-exposure Prophylaxis (PrEP) Among Men Who Have Sex with Men and Transgender Women in Brazil

Brenda Hoagland[1] · Raquel B. De Boni[1] · Ronaldo I. Moreira[1] · José Valdez Madruga[2] · Esper G. Kallas[3] · Silvia Pereira Goulart[2] · Natalia Cerqueira[3] · Thiago S. Torres[1] · Paula M. Luz[1] · Nilo Martinez Fernandes[1] · Albert Y. Liu[4] · Beatriz Grinsztejn[1] · Valdilea G. Veloso[1] · For the PrEP Brasil Study Team

Abstract Antiretroviral pre-exposure prophylaxis (PrEP) is recommended to prevent HIV infection among high-risk men who have sex with men (MSM) though not available in Brazil where the HIV epidemic persists unabated in this group. This cross-sectional study describes PrEP awareness and willingness and associated factors among MSM and transvestite/transgender women (trans women) pre-screened for the PrEP Brasil study. Awareness was reported by 61.3 % of the participants and was associated with age, education, site, study period and prior HIV testing. Most participants (82.1 %) were willing to use PrEP, which was associated with site, study period, number of male condomless anal sexual partners and anal sex with HIV positive/unknown partners. PrEP information is need among young and less educated individuals. Willingness to use PrEP was high and future studies should be conducted to confirm PrEP acceptability and the characteristics of the population who chose to adopt this intervention.

Keywords Pre-exposure prophylaxis · HIV prevention · MSM · Transvestite · Transgender women · Awareness · Willingness

✉ Brenda Hoagland
brenda.hoagland@ini.fiocruz.br

[1] Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz (INI/FIOCRUZ), Avenida Brasil 4365, Manguinhos, Rio de Janeiro 21040-360, Brazil

[2] Centro de Referência e Treinamento em DST/AIDS, São Paulo, Brazil

[3] Universidade de São Paulo, São Paulo, Brazil

[4] Bridge HIV, San Francisco Department of Public Health, San Francisco, CA, USA

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Introduction

Antiretroviral pre-exposure prophylaxis (PrEP), with either daily oral tenofovir disoproxil fumarate (TDF) or daily TDF in combination with emtricitabine (FTC), has been shown to be efficacious for HIV prevention for high-risk men who have sex with men (MSM), heterosexual men and women, discordant heterosexual couples and people who inject drugs [1–6]. The growing support for PrEP as a prevention tool has prompted a number of studies evaluating the willingness to use PrEP. Willingness to use PrEP, its uptake and patterns of adherence may vary across different geographic locations, with studies so far showing that 44–92 % of MSM were receptive to taking PrEP in both high and low/middle income countries [7–11].

Brazil has the largest population of individuals living with HIV/AIDS in Latin America [12], and a concentrated epidemic with an estimated HIV prevalence of 0.6 % in the general population (0.4 % among women and 0.8 % among men) and a 14.2 % prevalence among MSM [13]. Young MSM account for nearly 40 % of AIDS cases, with an increase of 41.3 % (aged 15–19 years) and 25.1 % (aged 20–24 years) observed in this group from 2004 to 2013 [14].

Although transgender women (trans women) represent a smaller population than MSM, they have extremely elevated HIV infection rates and very high risk for HIV infection [15]. Scarce data is available in Brazil on the HIV burden in the trans women population but reported HIV prevalence rates are high and driven by the interplay of several levels of HIV risks which contribute to a dynamic process of increased vulnerability to HIV/AIDS in this group [16, 17]. Thus, the HIV epidemic in Brazil persists unabated in MSM and trans women, with a high proportion of individuals remaining unaware of their HIV status [13].

In this context, the PrEP Brasil Study (NCT01989611), a multicenter, open-label, PrEP demonstration project, was designed to assess uptake, safety and feasibility of PrEP provided at no cost for high risk MSM and trans women through the Brazilian public health system (*Sistema Único de Saúde*—SUS). During the PrEP Brasil pre-screening phase, awareness and willingness to use PrEP and other prevention strategies for HIV were assessed. The aims of the present analysis are to describe: (1) PrEP awareness and its associated factors, as well as (2) PrEP willingness and its associated factors among MSM and trans women pre-screened for the PrEP Brasil study.

Methods

This study refers to the cross-sectional analysis of PrEP Brasil data collected at the pre-screening visit. PrEP Brasil was conducted in 3 sites: Fundação Oswaldo Cruz (Fiocruz) in Rio de Janeiro city (RJ), Centro de Referência e Treinamento em DST/AIDS (CRT-SP) and Universidade de São Paulo (USP), both in São Paulo city (SP). Information about the project was made widely available in newspapers, magazines, social media web site and a project homepage. Participants were either self-referred to the study or approached when seeking HIV testing, post exposure prophylaxis (PEP) or other health services. In Rio de Janeiro city, potentially eligible participants were also approached when seeking HIV testing at a Lesbian, Gay, Bisexual, Transgender Non-Governmental Organization (LGBT NGO) and at a mobile testing unit located in a LGBT friendly venue.

Study Population

A convenience sample of 1270 individuals, were accessed from April 01, 2014 to July 28, 2015. Inclusion criteria for the present study were male sex at birth, 18 years of age or more, any sexual intercourse with other men/trans women in the last 12 months, self-report of HIV negative status, and residency in RJ or SP. Individuals were ineligible for the following reasons: 2 were younger than 18 years of age, 5 did not live in the participating states, 3 were HIV positive, and 24 did not have sex with a male partner. Additionally, 49 individuals were excluded from this analysis because they were interviewed more than once (n = 26) or had missing data on the inclusion criteria (n = 23).

Measures

A self-administered questionnaire answered on tablets measured PrEP awareness and willingness and a face-to-face structured interview evaluated demographics and sexual risk-behavior. After that, an HIV rapid test was offered to all participants, although it was not mandatory at the pre-screening visit. For those who accepted HIV-1/2 Bio-Manguinhos® (Bio-Manguinhos/Fiocruz), HIV Rapid Check® (FAHUCAM) and HIV-1/2Bioeasy® (Standard Diagnostic Inc.) were performed, in accordance to the Brazilian official guidelines for HIV testing [18]. Individuals who were not tested at this visit (n = 51) and those with discordant samples (n = 1) were classified as not tested, for the purpose of the present analysis.

Main Outcomes

This study had two main outcomes: (1) PrEP awareness measured as a positive answer to the question "Have you ever heard about PrEP for HIV prevention?", and (2) Willingness to use PrEP defined as the "High interest" option on a four-point Likert scale to the question "What would be your level of interest in using PrEP if it was available through the Brazilian public health system (*Sistema Único de Saúde*—SUS)?". These questions were asked after a brief information about PrEP "PrEP is pre-exposure prophylaxis were medication is used daily to prevent HIV."

Variables

Demographics variables included were age (categorized in three groups: 18–24 years, 25–35 years and more than 36 years); self-reported skin color/race (white, black, mixed-black, native and Asian options were dichotomized to white/non-white following previous categorization used in Brazilian HIV studies [19, 20]), schooling (dichotomized to less than 12 years and 12 years or more), steady partner (yes/no) and site (Fiocruz, CRT-SP and USP). Gender was self-reported and dichotomized to 'Male' and 'Trans women'.

Risk perception for HIV was measured by the question "What is your chance of getting HIV in the next year?" with the possible options being None (0 %), Low, Some (50 %), High, Certainly (100 %), these options were dichotomized into Low (None and Low options) and High (Some, High and Certainly options). Prior HIV testing was evaluated in the past year (yes/no). Risk behavior for HIV was evaluated by the following questions: Number of condomless anal sex partners in the last 12 months (less than 2 and 2 or more), anal sex with HIV-positive partners in the last 12 months (yes/no/I don't know) and history of STD diagnosis in the last 12 months (yes/no).

Interview dates were categorized into two successive eight-month periods (April 2014–November 2014, December 2014–July 2015). In addition, awareness

(through the question "Have you ever heard of… to prevent HIV infection?") and willingness (through the question "In case it was available in Brazilian public health system (SUS), would you have great interest in using…for preventing HIV?) for other HIV prevention measures (in addition to PrEP as detailed above) including condoms, microbicide, circumcision, post-exposure prophylaxis (PEP) and HIV-self-testing were assessed. A brief explanation on the preventive measures was provided before these questions were asked. Finally, we assessed individuals' willingness to use PrEP even if they had to pay for it (measured using a five-point Likert scale). Compensatory behavior ("I would not use condoms if I used PrEP") was also investigated among individuals reporting willingness to use PrEP using a five-point agreement/disagreement Likert scale.

Statistical Analysis

Awareness and willingness to use PrEP as well as other HIV prevention measures are given as percentages. Logistic regression models were used to explore and quantify the association of factors with PrEP awareness and willingness. Variables with $p < 0.1$ in bivariate analysis were included in the initial adjusted models. The final adjusted models included variables that remained significant (at 5 % significance threshold) as well as variables that were considered confounders (i.e., those that changed the odds ratio estimate of any of the remaining variables by more than 10 %). The prevalence of HIV was calculated excluding missing cases (HIV rapid test 'not performed', n = 52).

Ethical Aspects

INI Evandro Chagas-FIOCRUZ institutional review board has approved this study (#CAAE08405912.9.1001.5262 at "Plataforma Brasil") and all study participants have signed an informed consent form. Institutional Review Boards at CRT-AIDS and USP also approved the study after first approval has been granted at Fiocruz.

Results

The final study sample was comprised of 1187 individuals, 95.3 % were male and 4.7 % were trans women. Median age was 29 years (IQR 24–36), 56.2 % were non-white and 63.4 % had 12 years of education or more. Compared to males, trans women had lower schooling (less than 12 years of education: trans women 78.6 % vs. Male 34.5 %, $p < 0.001$) and were less likely to have a steady partner (trans women 32.1 % vs. Male 49.0 %, $p = 0.013$). Trans women were mostly recruited at Fiocruz (n = 48, 85 %) compared to CRT-SP (n = 6, 10 %) and USP (n = 2, 1.3 %), (trans women 85.7 %, $p = 0.01$ vs. Male 68.1 %, $p = 0.008$). Males and trans women were not significantly different with respect to age, skin color/race or HIV rapid test result. Overall, HIV prevalence was 9.8 % (n = 111/1135).

Figure 1 shows awareness and willingness to use the different HIV prevention methods. The most commonly known method was condom (99.4 %) while the least known was microbicide (19.4 %); 728 participants (61.3 %) reported being aware of PrEP (Fig. 1, top panel) and 975 (82.1 %) reported they would be willing to use PrEP (Fig. 1, bottom panel).

Awareness of PrEP was reported more frequently among older individuals, as well as among those self-identifying as white or who had 12 years or more of education. Additionally, participants who were recruited at the USP site reported greater awareness of PrEP (all $p < 0.05$ in bivariate analyses). Individuals with a higher perceived risk of getting HIV in the next year, as well as those who reported having a prior HIV test, anal sex with an HIV-positive partner and a STD diagnosis in the last 12 months more frequently reported PrEP awareness (all $p < 0.05$). Only 47 % of the individuals who had a positive HIV test had heard of PrEP compared to 63 % of those with a negative test ($p < 0.001$).

In the adjusted model, factors independently associated with PrEP awareness were age, education, site, prior HIV test, and study period. Individuals aged 25–35 years (adjusted odds ratio—AOR 1.43; 95 % CI 1.07–1.93) and those with more than 36 years (AOR 1.93; 95 % CI 1.35–2.75) had a higher odds of PrEP awareness when compared to those younger than 24 years as well as those with higher education (AOR 1.78; 95 % CI 1.36–2.32). Additionally, participants from CRT-SP (AOR 1.52; 95 % CI 1.06–2.19) and USP (AOR 2.41; 95 % CI 1.53–3.81), and those enrolled in the second half of the study (AOR 1.52; 95 % CI 1.18–1.96) were more likely to report PrEP awareness (Table 1).

After receiving brief information about PrEP, most individuals (n = 975/1187, 82.1 %) reported they would have great interest in using PrEP if available through the Brazilian public health system; 150 (12.6 %) reported they would have some interest; 45 (3.8 %) reported little interest and 17 (1.4 %) reported no interest. Moreover, most individuals (n = 900; 75.8 %) would use PrEP even if they had to pay for it (Totally Agree: n = 460, 38.8 %, and Agree: n = 440, 37.1 %); 152 (12.8 %) neither agree or disagree; n = 66 (5.6 %) partially disagree and 69 individuals (5.8 %) totally disagree. Among those individuals who were willing to use PrEP (n = 975), most (n = 526, 53.9 %) reported total disagreement with the sentence "I

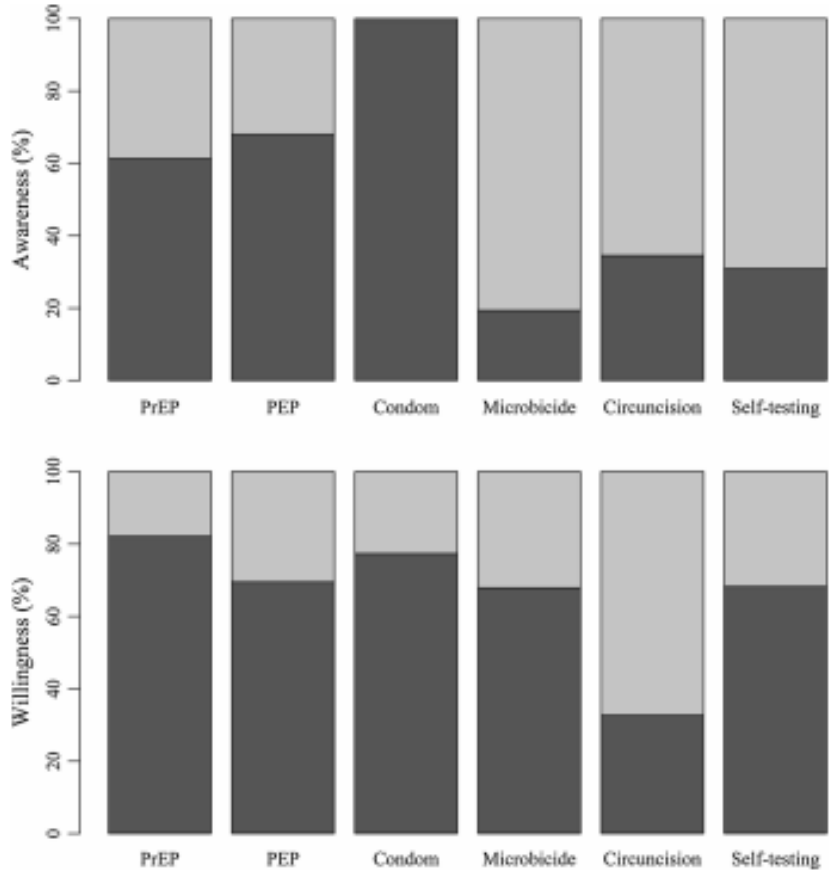

Fig. 1 Percentage of participants reporting awareness of (*top panel*) and willingness (*bottom panel*) to use PrEP as well as other HIV prevention methods

would not use condoms if I used PrEP", while only 38 (3.9 %) reported total agreement (171/17.5, 134/13.7 and 106/10.9 % reported partial disagreement, neither agree or disagree and partial agreement, respectively).

In the bivariate analysis (Table 2), most variables were associated with PrEP willingness, except for age, gender, steady partner and HIV test result. In the adjusted model, variables that remained independently associated with PrEP willingness were CRT-SP and USP sites (AOR 4.03; 95 % CI 2.12–7.77 and AOR 2.60; 95 % CI 1.35–4.99, respectively) compared to Fiocruz, high perceived likelihood of getting HIV over the next 12 months (AOR 1.42; 95 % CI 1.00–2.02), PrEP awareness (AOR 1.42; 95 % CI 1.03–1.94), two or more male condomless anal sexual partners (AOR 2.07; 95 % CI 1.47–2.91), anal sex with an HIV positive partner in the prior12 months (AOR 2.46; 95 % CI 1.60–3.78) and not knowing partner's HIV serostatus (AOR 1.46; 95 % CI 1.01–2.10) compared to not having an HIV positive partner.

Discussion

In this large contemporary study to investigate PrEP awareness and willingness in Brazil, PrEP awareness was reported by 61.3 % of participants. We found that PrEP awareness was associated with older age and higher education, with enrollment in São Paulo and in the second half of the study, as well as with having tested for HIV in the prior 12 months. Our study also showed substantial willingness to use PrEP (82.1 %), and found that willingness to use PrEP was associated with higher risk behavior, higher risk perception and previous PrEP awareness.

The present study shows that the observed level of PrEP awareness is similar to previous reported studies with MSM/trans women from different regions of the world notwithstanding the fact those studies were conducted 1 or 2 years earlier than ours [11, 21, 22]. We have also described awareness of other preventive measures such as condoms, PEP, microbicides, circumcision and HIV self-

Table 1 Sample characteristics by PrEP awareness

	Have you heard about PrEP for HIV prevention before?		Unadjusted				Adjusted			
	Yes	No	95 % CI				95 % CI			
	N = 728	N = 459	OR	Lower	Upper	*p* value	AOR	Lower	Upper	*p* value
Age										
18–24	168 (50.9)	162 (49.1)	Ref.				Ref.			
25–35	372 (64.1)	208 (35.9)	1.72	1.31	2.27	<0.001	1.43	1.07	1.93	0.02
≥36	188 (67.9)	89 (32.1)	2.04	1.46	2.84	<0.001	1.93	1.35	2.75	<0.001
Color										
White	357 (68.7)	163 (31.3)	1.75	1.37	2.22	<0.001	–			
Non-white	371 (55.6)	296 (44.4)	Ref.				–			
Schooling										
<12 years	206 (47.5)	228 (52.5)	Ref.				Ref.			
≥12 years	522 (69.3)	231 (30.7)	2.50	1.96	3.19	<0.001	1.78	1.36	2.32	<0.001
Gender										
Male	696 (61.5)	435 (38.5)	1.20	0.70	2.06	0.51	–			
Trans	32 (57.1)	24 (42.9)	Ref.				–			
Steadypartner										
Yes	360 (62.9)	212 (37.1)	1.14	0.90	1.44	0.27	–			
No	368 (59.8)	247 (40.2)	Ref.				–			
Site										
Fiocruz	442 (54.0)	376 (46.0)	Ref.				Ref.			
CRT-SP	163 (74.8)	55 (25.2)	2.52	1.80	3.53	<0.001	1.52	1.06	2.19	0.02
USP	123 (81.5)	28 (18.5)	3.74	2.42	5.76	<0.001	2.41	1.53	3.81	<0.001
Perceived likelihood of getting HIV in next year										
Low	420 (59.1)	291 (40.9)	Ref.				–			
High	308 (64.7)	168 (35.3)	1.27	1.00	1.62	0.05	–			
Prior HIV test in last 12 months										
Yes	552 (70.5)	231 (29.5)	3.10	2.41	3.97	<0.001	2.44	1.86	3.20	<0.001
No	176 (43.6)	228 (56.4)	Ref.				Ref.			
#Male condomless anal sexual partners in 12 months										
2 or more	349 (61.7)	217 (38.3)	1.03	0.81	1.30	0.82	–			
Less than 2	379 (61.0)	242 (39.0)	Ref.				–			
Anal sex with HIV positive partner in last 12 months										
No	143 (53.8)	123 (46.2)	Ref.				–			
Yes	261 (66.1)	134 (33.9)	1.68	1.22	2.30	0.001	–			
I don't know	324 (61.6)	202 (38.4)	1.38	1.02	1.86	0.03	–			
STD diagnosis last 12 months										
Yes	108 (68.8)	49 (31.2)	1.46	1.02	2.09	0.04	–			
No	620 (60.2)	410 (39.8)	Ref.				–			
HIV test result[a]										
Negative	642 (62.7)	382 (37.3)	Ref.				–			
Positive	52 (46.8)	59 (53.2)	0.52	0.35	0.78	0.001	–			
Not performed	34 (65.4)	18 (34.6)	1.12	0.63	2.02	0.70	–			
Interview date										
Apr'14–Nov'14	339 (56.9)	257 (43.1)	Ref.				Ref.			
Dec'14–Jul'15	389 (65.8)	202 (34.2)	1.46	1.15	1.85	0.002	1.52	1.18	1.96	0.001

Unadjusted and adjusted odds ratio (and 95 % confidence interval) for factors associated with PrEP awareness among individuals pre-screened in PrEP Brasil, 2014–2015

[a] Individuals who did not perform a rapid HIV testing in this visit (n = 51) and n = 1 individual with discordant samples were grouped as "not performed"

Table 2 Sample characteristics by willingness to use PrEP for HIV prevention

	Willing to use PrEP		Unadjusted 95 % CI				Adjusted 95 % CI			
	Yes N = 975	No N = 212	OR	Lower	Upper	*p* value	AOR	Lower	Upper	*p* va
Age										
18–24	268 (81.02)	62 (18.8)	Ref.				–			
25–35	474 (81.7)	106 (18.3)	1.03	0.73	1.46	0.85				
≥36	233 (84.1)	44 (15.9)	1.23	0.80	1.87	0.35				
Color										
White	446 (85.8)	74 (14.2)	1.57	1.15	2.14	0.004	–			
Non-white	529 (79.3)	138 (20.7)	Ref.							
Schooling										
<12 years	339 (78.1)	95 (21.9)	Ref.				–			
≥12 years	636 (84.5)	117 (15.5)	1.52	1.13	2.06	0.006				
Gender										
Male	925 (81.8)	206 (18.2)	0.54	0.23	1.27	0.16	–			
Trans	50 (89.3)	6 (10.7)	Ref.							
Steady partner										
Yes	467 (81.6)	105 (18.4)	0.94	0.70	1.26	0.67	–			
No	508 (82.6)	107 (17.4)	Ref.							
Fiocruz	628 (76.8)	190 (23.2)	Ref.				Ref.			
CRT-SP	207 (95.0)	11 (5.0)	5.69	3.04	10.67	<0.001	3.85	2.01	7.34	<0.0
USP-SP	140 (92.7)	11 (7.3)	3.85	2.04	7.26	<0.001	2.56	1.33	4.92	0.0
Perceived likelihood of getting HIV on the next 12 months										
Low	556 (78.2)	155 (21.8)	Ref.				Ref.			
High	419 (88.0)	57 (12.0)	2.05	1.47	2.85	<0.001	1.42	1.00	2.02	0.0
Prior HIV test on the last 12 months										
Yes	673 (86.0)	110 (14.0)	2.07	1.53	2.79	<0.001	–			
No	302 (74.8)	102 (25.2)	Ref.							
#Male condomless anal sexual partners in 12 months										
2 or more	500 (88.3)	66 (11.7)	2.33	1.70	3.20	<0.001	2.07	1.47	2.91	<0.0
Less than 2	475 (76.5)	146 (23.5)	Ref.				–			
Anal sex with HIV positive partner in last 12 months										
No	190 (71.4)	76 (28.6)	Ref.				–			
Yes	351 (88.9)	44 (11.1)	3.19	2.12	4.81	<0.001	2.37	1.54	3.65	<0.0
I don't know	434 (82.5)	92 (17.5)	1.89	1.33	2.67	<0.001	1.46	1.01	2.10	0.0
STD diagnosis last 12 months										
Yes	140 (89.2)	17 (10.8)	1.92	1.14	3.26	0.02	–			
No	835 (81.1)	195 (18.9)	Ref.							
HIV test result[a]										
Negative	839 (81.9)	185 (18.1)	Ref.				–			
Positive	91 (82)	20 (18)	1.00	0.60	1.67	0.99				
Not performed	45 (86.5)	7 (13.5)	1.42	0.63	3.19	0.40				
Interview date										
Apr'14–Nov'14	476 (79.9)	120 (20.1)	Ref.				–			
Dec'14–Jul'15	499 (84.4)	92 (15.6)	1.37	1.01	1.84	0.04				
PrEP awareness										
Yes	622 (85.4)	106 (14.6)	1.76	1.31	2.38	<0.001	1.42	1.03	1.94	0.0
No	353 (76.9)	106 (23.1)	Ref.				Ref.			

Crude and adjusted odds ratio for factors associated with willingness to use PrEP among individuals pre-screened in PrEP Brasil Stu 2014–2015

[a] Individuals who did not perform a rapid HIV testing in this visit (n = 51) and n = 1 individual with discordant samples were grouped as "I performed"

testing that might be related to the characteristics of the HIV epidemic in Brazil as well as to the availability of preventive interventions through the public health system. Interestingly, we found that if all technologies were available through SUS, over half the surveyed individuals would be very interested in using all of them, except for circumcision. This is a promising result in the context of combination approach to HIV prevention. Moreover, most participants (75.9 %) reported they would use PrEP even if they had to pay for it. Although Brazil has a well-known ARV universal access program for HIV treatment, the same does not happen for many other diseases. Thus, the population is used to paying out of pocket for medications in general. Nonetheless, taken together these results indicate that once available as a public health program PrEP will likely be used by MSM/trans women populations.

Our findings showing the association of PrEP awareness with older age and higher education highlight the need to increase access to PrEP information among young MSM/trans women, especially among the less educated. In Brazil, the HIV/AIDS epidemic is growing fast among youth [23], especially MSM [14] and lower education, may function as an additional barrier to access information on new preventive technologies. The association of prior HIV testing and PrEP awareness may be related to a higher risk perception among those who test more frequently, as well as to a higher exposure to prevention messages during testing-related counseling. Similarly, enrollment during the second half of the study as opposed to the first half was associated with higher odds of PrEP awareness, likely due to exposure to PrEP information through PrEP Brasil social media interventions as well as through articles in newspapers and magazines addressing the project. This point highlights the importance of building a strong component of community education within PrEP implementation programs in Brazil. It also highlights that strategies tailored to higher risk populations with low educational level and low health literacy who face additional barriers to access health services will be critical.

Similar to other studies conducted in high and low/middle income countries [9, 10, 24, 25] we found that most individuals would be willing to use PrEP. High risk behavior increased willingness to use PrEP, as described by others [25–29], as well as high risk perception of getting HIV. In particular, higher number of condomless anal sex partners was associated with willingness to use PrEP. Considering that the estimated HIV prevalence rates among MSM in Brazil ranges from 5.2 to 23.7 % [13, 30], with half of those HIV-infected being unaware of their serostatus [13], motivation could indeed be greater for taking PrEP in such context. As suggested by Golub [31], the subjective experience of risk-taking may vary by relational context. A sense of risk could be greater in serodiscordant relationships, especially in our context where, differently from other contexts, the knowledge of the HIV-positive partner's viral load is not usually used to guide sexual practices [32]. PrEP empowers users by allowing greater control over their HIV risk, rather than relying on partners to use condoms, take antiretroviral therapy, or accurately disclose their serostatus [33]. Results from qualitative research among heterosexual serodiscordant couples showed that PrEP was perceived as a solution to the threat of HIV transmission providing further stabilization for couples in serodiscordant relationships [34].

Interestingly, although the unadjusted analysis suggested that a prior STD diagnosis was associated with PrEP awareness (unadjusted odds ratio 1.46, 95 % CI 1.02–2.09) as well as with willingness to use PrEP (unadjusted odds ratio 1.92, 95 % CI 1.14–3.26) this association did not persist in the adjusted analyses. We hypothesize this is due to the fact that STDs are under diagnosed given that STD screening is not available through the Brazilian public health system. That is, despite WHO recommendations, the syndromic approach remains the standard of care thus not capturing asymptomatic infections, especially rectal chlamydia. The end result is many fewer opportunities for a patient-provider encounter where the patient could perceive his risk (not before acknowledged given his asymptomatic infection) and the role of STDs in HIV risk could be discussed.

Three important points are worthy of mentioning regarding the present study. First, our analysis highlighted differences in both PrEP awareness and willingness among sites in Rio de Janeiro and São Paulo. We hypothesize these differences are explained by participants' motivation when seeking the site. Considering n = 867 available answers, while at the Fiocruz site, in Rio de Janeiro, most individuals (n = 340, 61.7 %) were seeking HIV testing when assessed for the PrEP study, both at CRT-SP and USP, in São Paulo, most individuals were directly seeking participation in the PrEP Brasil study thus explaining their higher awareness and willingness (n = 149, 89.5 % and n = 129, 98.5 %, respectively). Second, PrEP Brasil assessed a trans women population (n = 56, 4.7 %) that is small but significantly higher than the proportion prescreened in other demonstration studies, such as the US PrEP demonstration project [21] and PrEP efficacy trials [35]. In a post hoc analysis of iPrEx trial, trans women participants had lower adherence despite presenting higher risk behaviors [36]. Demonstration studies designed for the trans women population and addressing their needs are urgently required in order to investigate PrEP engagement and its predictors in this population. Finally, increased condomless sex and participation in riskier sexual roles have been documented among PrEP users in PrEP demonstration projects and in hospital-based clinical

settings [37]. An increase in condomless sex with non-primary partners was also noted in the open label extension of the Partners PrEP Study [38]. In our study, among the 975 individuals who reported willingness to use PrEP, 144 (14.8 %) partially/totally agree with the sentence "I would not use condoms if I used PrEP", a fraction that resembles that from other PrEP acceptability studies [11, 39]. Predicted increases in sexual risk behavior among PrEP users may function as a barrier to access for reasons such as reduced motivation to seek PrEP or to sustain PrEP use for fear of stigmatization [40], stigma-related misperceptions of self-eligibility or need for PrEP and reduced willingness to prescribe PrEP among providers [41]. Also, fostering shame of sexual practices under the rubric of 'risk compensation' can jeopardize PrEP implementation and adherence [33]. Ideally, PrEP should be targeted to individuals who are at high risk of acquiring HIV, and this includes those who intentionally or not end up not using condoms consistently. The high degree of protection provided by PrEP when properly used likely outweighs the increased risk of HIV acquisition resulting from increased risk taking [42]. As such, hindering access to PrEP could prevent a net reduction in HIV risk even for individuals who increase their sexual risk behavior [43].

A recent study evidencing un-prescribed use of Truvada in some settings [45] warrants attention given the high willingness to use PrEP found in our sample. In Brazil, despite non-availability of Truvada for HIV treatment, tenofovir and lamivudine are available through the Brazilian Public Health System for treatment and post-exposure prophylaxis. Impeding access to PrEP may lead potential PrEP candidates to obtain these drugs, which were not evaluated in clinical trials for PrEP, in at least two ways: from an HIV-infected individual or by claiming recent exposure to HIV [45]. In either scenario, drug use would happen without any counseling or medical supervision.

The study has limitations. First, the sample is not probabilistic and data may not be generalized to all Brazilian MSM and trans women. However, it is important to note that some results, like HIV prevalence are similar to other Brazilian studies, meaning that the sample may have similarities with the population of MSM from Rio de Janeiro and São Paulo. Second, given the cross-sectional nature of the data, causality and the direction of association may not be inferred. Third, as in all self-reported behavioral studies, social desirability bias may not be ruled out, although self-answering study questionnaire on a tablet may have partially mitigated this effect. Fourth, the small number of trans women in our study population prevented us from stratifying the analysis to the trans women population. Fifth, we can't exclude that some individuals had PrEP awareness due to previous participation on the iPrEx/iPrEx OLE studies [1, 44] conducted in sites from RJ and SP. Finally, we have measured intention to use PrEP as a proxy of willingness. There are different methods for accessing PrEP awareness and willingness, as reviewed by Young and McDaid [46] and as such our results should be interpreted with care.

In summary, this study showed that willingness to use PrEP was high among MSM/trans women, and its association with riskier behavior is reassuring as it indicates that those individuals who are at higher risk of HIV infection are interested in this new prevention strategy. Efforts to increase access of young and less educated MSM/trans women to PrEP information must be implemented in Brazil. Finally yet importantly, PrEP studies tailored to trans women population are urgently needed.

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Compliance with Ethical Standards INI Evandro Chagas-FIOCRUZ institutional review board has approved this study (#CAAE08405912.9.1001.5262 at "Plataforma Brasil") and all study participants have signed an informed consent form. Institutional Review Boards at CRT-AIDS and USP also approved the study after first approval has been granted at Fiocruz.

Conflict of interest Albert Liu has participated in trials in which study drug and support for drug level testing were provided by Gilead Sciences.

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3 SEGUNDO ARTIGO

Autores:

Brenda Hoagland[1], Ronaldo I. Moreira[1], Raquel De Boni[1], Esper G. Kallas[3], José Valdez Madruga[2], Ricardo Vasconcelos[3], Silvia Goulart[2], Thiago S. Torres[1], Luana M. S. Marins[1], Peter L. Anderson[5], Paula Mendes Luz[1], Iuri da Costa Leite[1], Albert Y. Liu[4], Valdilea G.Veloso[1] and Beatriz Grinsztejn[1]

[1]Instituto Nacional de Infectologia Evandro Chagas, FIOCRUZ. Rio de Janeiro, Brazil

[2]Centro de Referência e Treinamento em DST/AIDS, São Paulo, Brazil

[3]Universidade de São Paulo, Brazil

[4] Bridge HIV, San Francisco Department of Public Health, San Francisco, USA

[5]University of Colorado Denver, Aurora, CO 80045, USA

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Research article

High pre-exposure prophylaxis uptake and early adherence among men who have sex with men and transgender women at risk for HIV Infection: the PrEP Brasil demonstration project

Brenda Hoagland[1], Ronaldo I. Moreira[1], Raquel B. De Boni[1] Esper G. Kallas[2], José Valdez Madruga[3], Ricardo Vasconcelos[2], Silvia Goulart[3], Thiago S. Torres[1], Luana M. S. Marins[1], Peter L. Anderson[4], Paula M Luz[1] Iuri da Costa Leite[1], Albert Y. Liu[5], Valdilea G. Veloso*[1] and Beatriz Grinsztejn *[1§] for the PrEP Brasil Study Team

[§]Corresponding author: Beatriz Grinsztejn, INI/FIOCRUZ, Avenida Brasil 4365, Manguinhos, Rio de Janeiro 21040-360, Brazil. Tel: 55-21-3865-9128. gbeatriz@ini.fiocruz.br
*Contributed equally as last authors
Clinical Trial Number 01989611

Abstract

Introduction: The efficacy of pre-exposure prophylaxis (PrEP) in preventing sexual acquisition of human immunodeficiency virus (HIV) is well established. Little is known about the feasibility of PrEP implementation in middle-income settings with concentrated epidemics among men who have sex with men (MSM) and transgender women (TGW).

Methods: PrEP Brasil is a prospective, multicentre, open-label demonstration project assessing PrEP delivery in the context of the Brazilian Public Health System. HIV-uninfected MSM and TGW in 3 referral centres in Rio de Janeiro and São Paulo were evaluated for eligibility and offered 48 weeks of daily emtricitabine/tenofovir for PrEP. Concentrations of tenofovir diphosphate in dried blood spot samples (DBS) at week 4 after enrolment (early adherence) were measured. Predictors of drug levels were assessed using ordinal logistic regression models considering the DBS drug level as a 3 level variable (<350 fmol/punch, ≥350–699 fmol/punch and ≥700 fmol/punch).

Results: 1,270 individuals were assessed for participation; *n* = 738 were potentially eligible and *n* = 450 were offered PrEP (PrEP uptake was 60.9%). Eligible but not enrolled individuals were younger, had lower HIV risk perception and had lower PrEP awareness. At week 4, 424 participants (of the 450 enrolled) had DBS TFV-DP concentrations, 94.1% in the protective range (≥350 fmol/punch, consistent with ≥2 pills per week), and 78% were in the highly protective range (≥700 fmol/punch, ≥4 pills per week). Participants with ≥12 years of schooling had 1.9 times the odds (95%CI 1.10–3.29) of a higher versus lower drug level than participants with <12 years of schooling. Condomless receptive anal intercourse in the prior 3 months was also associated with higher drug levels (adjusted OR = 1.78; 95% CI 1.08–2.94).

Conclusions: The high uptake and early adherence indicate that PrEP for high-risk MSM and TGW can be successfully delivered in the context of the Brazilian Public Health System. Interventions to address disparities on PrEP awareness and HIV risk perception among the younger and less educated are urgently needed in order to maximize the impact of this prevention strategy on the reduction of HIV infection among MSM and TGW in Brazil.

Keywords: Pre-exposure prophylaxis; HIV prevention; MSM; transgender women; PrEP uptake; PrEP adherence; DRUG Levels

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Introduction

The effectiveness of oral pre-exposure prophylaxis (PrEP) using tenofovir/emtricitabine (TDF/FTC) for prevention of sexually acquired human immunodeficiency virus (HIV) infection for men who have sex with men (MSM) and transgender women (TGW) has been demonstrated in randomized trials and open-label studies [1–5]. PrEP effectiveness results from achieving protective drug levels in the blood which is directly related to the level of adherence to the medication use [1,6,7]. In the iPrEx study, protection was estimated to be over 90% in those with detectable drug levels in their blood [1], with pharmacokinetic modelling suggesting that efficacy reaches 96 and 99% with dosing of four and seven days per week, respectively [8]. Subsequent results from the open-label extension of the iPrEx study estimated that 90% protection was achieved with 2–3 drug doses/week and that 4 or more doses/week were highly protective against HIV infection [9]. Similarly, Cottrell et al., in a study that combined an *in vitro* efficacy target with mucosal tissue pharmacokinetic data and mathematical modelling, also found that 2 doses/week resulted in effective colorectal concentrations in

>95% of the population [10]. Drug levels consistent with the intake of 4 or more pills/week were observed in only about one-third of study follow-up visits in iPrEx OLE [11], corroborating that adherence is a significant challenge to PrEP effectiveness.

International guidelines were released recommending PrEP for MSM and TGW at "substantial risk" for acquiring HIV [12,13]. However, PrEP is not widely available and the feasibility of this prevention strategy in real world settings from low- and middle-income countries is unknown. As of December 2016, no country in Latin America had implemented PrEP as a public health policy. In Brazil, specifically, PrEP can only be obtained in the context of research or through a commercial vendor. The HIV epidemic in Brazil persists unabated in the MSM and TGW populations [14]. While HIV prevalence among the general population is 0.6%, in MSM it reaches 14.2% [14]. TGW represent a smaller population than MSM, nevertheless they have extremely elevated HIV infection rates [15].

PrEP Brasil is a multicentre, open-label PrEP demonstration project to assess the uptake, adherence, safety, and feasibility of PrEP implementation provided at no cost to high-risk MSM and TGW in the context of the Brazilian public health system. In this manuscript, we describe PrEP uptake and early adherence [16] assessed by TDF/FTC drug levels (i.e. tenofovir-diphosphate and FTC-triphosphate) measured in dried blood spots (DBS) at week 4 after enrolment and its associated factors in the PrEP Brasil demonstration study. Additionally, we describe baseline demographic and risk characteristics of the study population.

Methods

Study design, sites, and study population

PrEP Brasil is a 48-week prospective, longitudinal, open-label demonstration study assessing PrEP delivery at three reference centres for HIV prevention and care in Rio de Janeiro (RJ) and São Paulo (SP), the two cities in Brazil with the highest burden of HIV cases [17]. Study sites are Fundação Oswaldo Cruz (FIOCRUZ) in RJ, Universidade de São Paulo (USP) and Centro de Referência e Treinamento em DST e AIDS (CRT-SP), both in SP. All the three sites have outstanding expertise in providing HIV prevention and care services in the context of Brazilian Public Health System (SUS). In addition, these sites conduct research in the HIV field. In RJ, individuals seeking testing at Arco Iris, a lesbian, gay, bisexual, transgender (LGBT) non-governmental organization (NGO), and at a mobile testing unit located at a LGBT-friendly venue were also assessed for potential eligibility for PrEP Brasil and subsequently referred to FIOCRUZ for screening. Social media and other media were used by the 3 sites to advertise the project and a website was constructed (www.prepbrasil.com.br). Individuals were assessed for participation from 1 April 2014 to 28 July 2015, enrolled from 4 June 2014 to 28 July 2015, and collection of week 4 results ended in 24 August 2015.

Eligibility criteria

Eligibility criteria included ≥18 years of age, male sex at birth, residence in RJ or SP, reporting sex with male or TGW and any of the following sexual risk criteria in the prior 12 months: ≥2 episodes of condomless anal sex, ≥2 episodes of anal sex with an HIV-infected partner, or history of STD diagnosis. Individuals were ineligible, if presenting with any of the following criteria: a positive HIV rapid test, creatinine clearance <60 ml/min, proteinuria (urine dipstick 1+ or more), a positive Hepatitis B surface antigen (HBsAg) serology test, a severe medical comorbidity, use of antiretrovirals (ARV), interferon or interleukin, or failure to provide contact information or return for enrolment within 45 days of the screening visit.

Study procedures

Individuals either self-referred or clinic referred to take part in PrEP Brasil when searching for HIV testing, post exposure prophylaxis (PEP) or health services.

At the pre-screening visit, a self-answered structured interview using tablets assessed demographics, HIV risk perception, sexual risk entry criteria, self-reported HIV serostatus, awareness and willingness to use PrEP and other HIV prevention methods. HIV rapid testing was offered [18]. In addition, individuals with a negative HIV rapid test who reported condomless anal intercourse in the last 30 days were offered pooled or individual HIV RNA testing (pooled RNA in RJ and individual RNA in SP) to diagnose acute HIV infection. Potentially eligible individuals were invited to participate in PrEP Brasil. There was no pre-determined timeframe between pre-screening and screening visits, but individuals were encouraged to show-up for screening within one week of pre-screening. Refusal reasons were noted.

At the screening visit, participants were informed about study procedures and visit schedule. Laboratory assessments included HIV rapid testing, pooled or individual HIV RNA, HBsAg, hepatitis C antibody, syphilis, creatinine clearance and proteinuria (urine dipstick 1+ or more). Potential participants received a thorough explanation of the potential risks and benefits of FTC/TDF for PrEP as well as the importance of study drug adherence and risk reduction counselling.

The enrolment visit of eligible individuals was scheduled within 45 days of the screening visit. At this visit, HIV rapid test and pooled or individual HIV RNA were performed, as well as creatinine clearance and proteinuria (urine dipstick 1+ or more). A rectal sample was collected for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoea* (NG) detection. Participants answered a computer-assisted self-interview (CASI) including demographics, sexual and drug-use behaviour questions. Eligible individuals were offered daily oral PrEP with TDF/FTC.

At week 4 visit, HIV testing (rapid test and pooled or individual HIV RNA), creatinine clearance and proteinuria (urine dipstick 1+ or more), clinical evaluation and DBS collection for tenofovir-diphosphate (**TFV-DP**) and FTC-triphosphate (**FTC-DP**) assessments were performed. Individuals could formally refuse to participate in any of

the visits, or simply not show up in the subsequent scheduled visit.

Laboratory procedures

HIV testing was performed following the Brazilian Ministry of Health algorithm [19]. Briefly, two different HIV rapid tests were performed when the first test was positive. If the second test was positive, individuals were considered HIV infected; if the second test was negative, individuals were considered indeterminate. Individuals with a first negative test were classified as HIV uninfected. Pooled or individual HIV RNA was performed at screening, enrolment and at each study visits thereafter.

A rapid plasma reagin (RPR) test was performed for syphilis screening; positive results were confirmed using a microhemagglutination assay for *Treponema pallidum* (MHA-TP). Active/recent syphilis was defined as titres ≥1/8 and a positive MHA-TP (WAMA Diagnóstica, SP). Rectal *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoea* (NG) detection was performed using the Abbott Real Time platform and the NG/CT Amplification Reagent Kit (Abbott Molecular, Des Plains, IL). All indeterminate results for rectal CT/NG were repeated using the same tests on the same sample. If the repeated test was conclusive, the results were reported accordingly. If remained indeterminate, results were reported as negative. All rectal CT and NG samples were processed at the FIOCRUZ Laboratory.

Measures

Socio-demographic

Age was categorized in 3 strata: 18–24 years; 25–34 years and ≥35 years; skin colour/race (white, black, mixed-black, native, Asian) were categorized in white, black and mixed; schooling was dichotomized in <12 years and ≥12 years (12 years is equivalent to completing high school education in Brazil) and the sites were grouped accordingly to geographical locations (RJ and SP). Gender was considered as "Male" and TGW. Housing situation, assessed at enrolment using CASI, was dichotomized as rent/own housing or other (living with friends or family, living in public housing). Individuals were asked if they had a steady partner and answered yes/no at their own discretion.

Sexual behaviour and sexually transmitted diseases

All variables related to sexual behaviour refer to the prior 3 months and were assessed at enrolment using CASI; these questions refer to the participant's prior 3 partners. Those who responded that any of the 3 prior partners was a "client" were considered as having sex with clients. Similarly, dichotomous variables were created for condomless receptive anal intercourse and for sex with an HIV-positive partner. The number of male, TGW and female partners was assessed, as well as the possible sexual roles with these partners ("Insertive", "Receptive" or "Both"). A dichotomous variable "STD diagnosis" was created considering any positive laboratorial diagnosis for syphilis, gonorrhoea or chlamydia.

Substance use, mental health, and hormone use

Binge drinking [20] was evaluated with the question "In the last 3 months, did you drink 5 or more drinks in a couple of hours?" "Any illicit drug" considered the use of any of the following: marijuana, stimulants (cocaine, crack, amphetamines), hallucinogens (solvents, LSD, ketamine) and opioids (heroin, methadone), which were shown in a pre-defined list of all substances participants could have used in the prior 3 months. The list also included non-medical use of tranquilizers and erectile dysfunction drugs. Use of any injectable substance (IDU) was also assessed. Depression was screened using the Patient Health Questionnaire-2 (PHQ-2) using a score ≥3 as the cut-off for a positive screen [21,22]. For TGW, hormone use was captured as concomitant medication use at the enrolment visit.

Risk perception

In the pre-screening interview, risk perception was assessed by the question "What is your chance of getting HIV in the next year?" with possible options dichotomized into Low (None/Low) and High (Some/High/Certainly). Additionally individuals were asked about previous HIV testing in the prior year (Yes/No). At enrolment, the number of HIV tests (with possible answers 0, 1–3, >3) in the last 12 months was considered as a proxy of risk perception, as well as the reported use of post-exposure prophylaxis (PEP).

Safety monitoring

All adverse events were graded using the Division of AIDS (DAIDS) Adverse Event Grading Table [23]. Clinical symptoms, including gastrointestinal (GI) symptoms were evaluated at week 4 and were dichotomized (Yes/No) indicating the presence of at least one of the following: abdominal pain, diarrhoea, flatulence, nausea and vomiting. Proteinuria and creatinine clearance were assessed at screening, enrolment and week 4 visits.

Main outcome

TFV-DP and FTC-TP were assessed for all study participants at week 4 in DBS cards using liquid chromatography and mass-spectroscopy (LC/MS/MS). Our main outcome of interest was early adherence as measured by TFV-DP drug levels at week 4. In addition, descriptive results of the FTC-TP levels are presented. DBS samples were stored at −20°C within 24 h of collection and shipped on dry ice to the University of Colorado Antiviral Pharmacology Laboratory after study enrolment was finalized. Three millimetres punches were extracted and analyzed for TFV-DP and FTC-TP by LC/MS/MS, as previously described [2,24,25]. Week 4 values were used to estimate steady-state values based on a 17-day half-life for interpretation. For the purposes of the statistical analysis, a 3-level ordinal variable classifying participants as TFV-DP <350fmol/punch (<2 doses/week), ≥350–699 fmol/punch (2–3 doses/week-protective range) or ≥700 fmol/punch (≥4 doses/week; highly protective range) was created. This categorization of TFV-DP concentrations was used in the iPrEx Open Label Extension [2] and derived from previous pharmacokinetic modelling studies [8].

Statistical analysis

Variables describing the characteristics of potentially eligible individuals (enrolled and not enrolled), as well as enrolled participants by site location are presented in terms of absolute numbers and proportions, when categorical, and median and interquartile range when continuous. Distributions were compared using chi-square test, Fisher exact test or Kruskal–Wallis statistics, as appropriate. PrEP uptake was defined as the number of participants enrolled divided by the number of potentially eligible participants at the pre-screening visit minus the clinical ineligible participants (at screening and enrolment visits) [26]. Factors associated with PrEP uptake were evaluated using logistic regression model while predictors of drug levels were assessed using ordinal logistic regression models considering the DBS drug level as a 3 level variable (<350 fmol/punch, ≥350–699 fmol/punch and ≥700 fmol/punch). Only variables statistically significant at 5% in the unadjusted models were kept in the adjusted models. The use of the ordinal logistic regression model requires that the effect of each predictor is the same for different logit function, that is, the odds ratio comparing the odds of high drug levels (≥4 doses) to the odds of medium-low drug levels (2–3 doses and <2 doses) is the same as that obtained when the comparing the odds of high-medium drugs levels (≥4 doses and 2–3) to the odds of low drug levels (<2 doses). This proportional odds assumption was evaluated using the SCORE test [27]. The results of the logistic ordinal model were then reported in terms of odds ratio (OR), which can be interpreted as the effect of the variable on the odds of being in a higher versus lower category of drug levels. The association of GI symptoms and drug levels at week 4 was evaluated using ordinal logistic regression models [28]. Additionally, to explore possible effects of hormone use on TFV-DP levels among TGW, two modelling approaches were used: (1) a logistic regression model with ≥4 doses/week as the outcome and use/non-use of hormone as the dichotomous explanatory variable, (2) a linear regression model with TFV-DP concentration as the continuous outcome variable and use/non-use of hormone as the dichotomous explanatory variable. Analyses were performed using PROC GENMOD available in the Software SAS [27].

Ethical aspects

Institutional review boards at each site approved the study and all study participants signed an informed consent form at pre-screening and screening visits.

Results

Overall, 1270 individuals were assessed at the pre-screening visit at the 3 sites. Of these, 517 (40.7%) were ineligible, and 753 (59.3%) were potentially eligible and invited to participate in PrEP Brasil. Among the 18 that refused to participate, the main refusal reasons were lack of time and fear of side effects. In total, 232 (232/753; 30.8%) potentially eligible individuals who accepted to participate did not show up for the screening visit and 18 declined, leading to 503 (503/1270; 39.6%) screened individuals. There were 8 screening failures, two of which were acute HIV infections. Thus, the prevalence of acute infection at the screening visit was 0.4% (2/503 × 100). In addition, one individual at pre-screening had a diagnosis of acute HIV infection (negative HIV rapid test and a detectable HIV RNA). Twenty-four individuals did not show up, 3 declined to be enrolled and 468 were evaluated for enrolment. Of these, 11 declined enrolment during the visit and 7 individuals were deemed ineligible. In the end, 450 participants were enrolled (450/1270; 35.4%) (Figure 1). The final number of potentially eligible participants (738) used for PrEP uptake calculations was given by the initial 753 minus the subsequent 15 participants who were subsequent deemed ineligible during screening and enrolment visits.

PrEP uptake was 60.9% (450 enrolled/738 potentially eligible). Most of the potentially eligible individuals were self-referred (n = 310/559 available answers; 55.5%) and 249 were clinic referrals (249/559; 44.5%). Table 1 depicts the characteristics of potentially eligible individuals stratified by enrolment status (uptake). Variables significantly associated with showing up to the screening visit were the same as those associated with uptake (Supplementary Table 1). Compared to those enrolled, a higher proportion of eligible but not enrolled individuals was younger, less educated, more frequently self-defined as of mixed race, had lower HIV risk perception, lower prior HIV testing rates, lower PrEP awareness and was less likely to report anal sex with partners of unknown HIV status (all $p < 0.05$). According to the adjusted logistic regression model, factors independently associated with uptake were site location (aOR = 5.03; 95% CI: 3.37–7.50, SP compared to RJ), perceiving a 50–100% chance of getting HIV in the next year (aOR = 1.44; 95% CI: 1.03–2.02) and having prior PrEP awareness (aOR = 2.19; 95% CI: 1.52–3.16).

From the 450 enrolled participants, 265 (76.8%; 265/345 available answers) were self-referred and 80 (23.2%; 80/345) were clinic referrals. Baseline characteristics for the 450 enrolled participants according to site location are shown in Table 2. Median age was 30 years (interquartile range (IQR) 24–35 years), the majority self-referred as white (n = 243, 54%) and reported their living situation as rent or own housing (n = 289, 64.2%). Forty per cent (n = 180) of the enrolled individuals were from RJ, most had ≥12 years of education (n = 335, 74.4%), and reported a steady partner (n = 254, 56.4%). Overall, 94.7% of the participants were male (89.9% self-identified as gay) and 5.3% were TGW. All demographic characteristics, except reporting a steady partner, were significantly different ($p < 0.05$) between site locations.

The median number of male anal sex partners in the previous 3 months was 3 (IQR 1–10) and none of the participants reported sex with TGW or women. Most (n = 284, 63.1%) reported both receptive and insertive anal sex and 44.7% (n = 201) reported condomless receptive anal intercourse in previous 3 months and these behaviours were not significantly different across sites. Any STD at screening/enrolment was diagnosed in 20% (89/444) of the participants: 9.6% (43/444) with active/recent syphilis, 4.9% with rectal

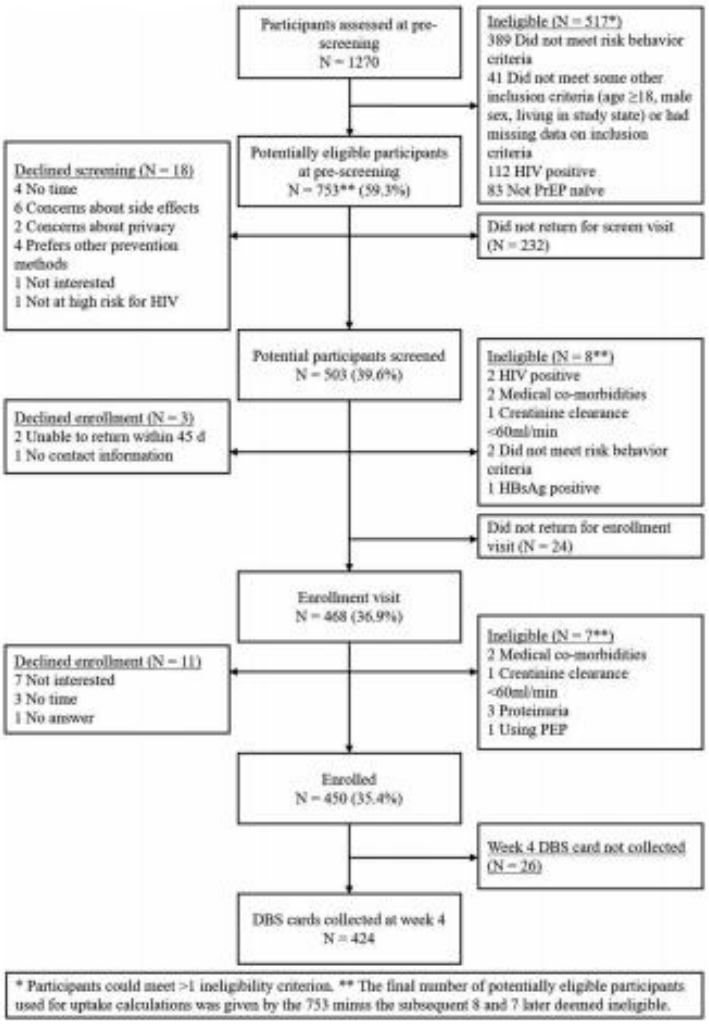

Figure 1. Inclusion flowchart - PrEP Brasil, 2014-15.

gonorrhoea (22/444) and 8.1% (36/444) with rectal chlamydia. Any illicit drug use in the prior 3 months was reported by 29.9% (134/447), and the most frequent drugs reported were marijuana (128/450, 28.4%) and stimulants (62/450, 13.7%). IDU was reported by 1.1% (5/450). Stimulant use was more prevalent in SP ($p = 0.01$).

From the 450 enrolled participants, 26 (5.8%) did not collect DBS at week 4. For the 424 (94.2%) participants who had DBS samples at week 4: 5.9% ($n = 25$) had TFV-DP level consistent with <2 doses/week, 15.6% ($n = 66$) with 2–3 doses/week and 78.5% ($n = 333$) were in the highly protective range, corresponding to ≥4 doses/week. Almost 90% of the participants (379/424) had FTC-TP detectable concentrations at week 4, indicating dosing within the last 48 h [24]. Table 3 presents participant's characteristics according to drug levels, the unadjusted and adjusted factors associated with higher drug levels. Results from the unadjusted models showed that the assumption of proportional odds was upheld for all variables as the p-values are higher than 0.05. Four variables were statistically significant at 5% ($p < 0.05$): site location, colour/race, schooling and condomless receptive anal intercourse in the prior 3 months. The odds of achieving a higher versus lower drug level by site location were attenuated in the adjusted model (aOR = 1.66 for SP compared with RJ; 95% CI: 0.97–2.84). The loss of significance of site location was explained by the inclusion of schooling in the model, as the proportion of participants with ≥12 years schooling in SP (87.4%) was much higher than in RJ (55%). In fact, in the adjusted

Table 1. Characteristics of potentially eligible individuals by enrolment status, PrEP Brasil

	Overall	Uptake		Unadjusted		Adjusted	
	Potentially eligible individuals N=738* (%)	Enrolled N=450 (%)	Not enrolled N=288(%)	OR	p-value	aOR	p-value
Site Location							
RJ	413 (56.0)	180 (40.0)	233 (80.9)	1	-	1	-
SP	325 (44.0)	270 (60.0)	55(19.1)	6.35(4.48-9.01)	<0.01	5.03 (3.37-7.50)	<0.01
Age							
18-24 years	210 (28.5)	113 (25.1)	97 (33.7)	0.54 (0.36-0.82)	<0.01	0.78 (0.49-1.25)	0.30
25-34 years	348 (47.2)	214 (47.6)	134 (46.5)	0.74(0.51-1.08)	0.12	0.77 (0.50-1.19)	0.24
>=35 years	180 (24.3)	123 (27.3)	57 (19.8)	1	-	1	-
Schooling							
< 12 years	227 (30.8)	115 (25.6)	112 (38.9)	1	-	1	-
≥ 12 years	511 (69.2)	335(74.4)	176 (61.1)	1.85(1.35-2.55)	<0.01	0.89 (0.60-1.31)	0.56
Color/Race							
White	358 (48.5)	243 (54.0)	115 (40.0)	1	-	1	-
Black	102 (13.8)	57 (12.7)	45 (15.6)	0.60 (0.38-0.94)	0.02	1.26 (0.75-2.12)	0.37
Mixed**	272 (36.9)	145 (32.2)	127 (44.1)	0.54(0.39-0.75)	<0.01	0.98 (0.66-1.43)	0.90
Gender							
Male	703 (95.3)	425 (94.4)	278 (96.5)	1	-	-	-
TGW	35 (4.7)	25 (5.6)	10 (3.5)	1.64 (0.77-3.46)	0.20	-	-
Steady Partner							
Yes	376 (51.9)	233 (53.3)	143 (49.8)	1.15 (0.85-1.55)	0.36	-	-
No	348 (48.1)	204 (46.7)	144 (50.2)	1	-	-	-
Perceived likelihood of getting HIV in the next year							
0-25%	377 (52.1)	205 (46.9)	172 (59.9)	1	-	1	-
50-100%	347 (47.9)	232 (53.1)	115 (40.1)	1.69 (1.25-2.29)	<0.01	1.44 (1.03-2.02)	0.03
Previous HIV test (12 months)							
Yes	538 (74.3)	359 (82.2)	179 (62.4)	2.78 (1.97-3.91)	<0.01	1.36 (0.91-2.03)	0.13
No	186 (25.7)	78 (17.8)	108 (37.6)	1	-	1	-
Prior PrEP awareness							
Yes	466 (64.1)	328 (74.5)	138 (48.1)	3.16 (2.31-4.34)	<0.01	2.19 (1.52-3.16)	<0.01
No	261 (35.9)	112 (25.5)	149 (51.9)	1	-	1	-
# male condomless a-I sex partners (last 12 months)							
<2	252 (34.8)	143(32.7)	109 (38.0)	1	-	-	-
2 or more	472 (65.2)	294(67.3)	178 (62.0)	1.26 (0.92-1.72)	0.15	-	-
A-I sex with HIV-positive partners							
Yes	360 (49.7)	223(41.0)	137 (47.8)	1.38 (0.90-2.13)	0.14	-	-
No	97 (13.4)	47 (10.8)	50 (17.4)	1	-	-	-
I do not know	267 (36.9)	167(38.2)	100 (34.8)	1.42 (0.91-2.22)	0.12		
STD history (12months)							
Yes	139 (19.2)	87 (19.9)	52 (18.1)	1.12 (0.77-1.64)	0.55	-	-
No	585 (80.8)	350(80.1)	235 (81.9)	1	-	-	-

TGW= Transgender women, STD =Sexually transmitted diseases, RJ = Rio de Janeiro, SP= São Paulo.
*For 16 participants, data obtained by ACASI interview in pre screening were not properly synchronized resulting in missing values. Missing information were fully recovered for Site, Age, Schooling and Race, and partially recovered for Gender and Prior PrEP awareness.** Category composed of "yellow and indigenous"

Table 2. Participants characteristics at enrolment by site location. PrEP Brasil-2015

Participant's characteristics	Total	RJ	SP	Chi-Square
Overall	**450**[1]	**180 (40.0%)**	**270 (60%)**	<0.01
Socio-demographics[2]				
Age				0.02
18–24 years	113	58 (32.2%)	55 (20.4%)	
25–35 years	214	76 (42.2%)	138 (51.1%)	
≥35 years	123	46 (25.6%)	77 (28.5%)	
Colour/Race				<0.01
White	243	60 (33.5%)	183 (68.8%)	
Black	57	41 (22.9%)	16 (6.0%)	
Mixed Race	145	78 (43.6%)	67 (25.2%)	
Schooling				<0.01
<12 years	115	81 (45.0%)	34 (12.6%)	
≥12 years	335	99 (55.0%)	236 (87.4%)	
Gender				<0.01
Male	425	161 (89.4%)	265 (97.8%)	
Trans women	25	19 (10.6%)	6 (2.2%)	
Housing situation				<0.01
Rent or own housing	289	98 (55.7%)	191 (71.5%)	
Other (live with friends/family, live in public housing)	154	78 (44.3%)	76 (28.5%)	
Steady partner				0.51
Yes	254	105 (58.3%)	149 (55.2%)	
No	196	75 (41.7%)	121 (44.8%)	
Sexual behaviour in last 3 months				
Had sex with client				0.63
Yes	27	12 (6.7%)	15 (5.6%)	
No	423	168 (93.3%)	255 (94.4%)	
Unprotected receptive anal intercourse				0.28
Yes	201	86 (47.8%)	115 (42.6%)	
No	249	94 (52.2%)	155 (57.4%)	
Sex with HIV-positive partners				0.11
Yes	223	80 (46.5%)	143 (54.4%)	
No	212	92 (53.5%)	120 (45.6%)	
Median Number of male partners (IQR)	3 (1–10)	3 (1–10)	4 (1–10)	0.22 [3]
Sexual role with male partners				0.29
Insertive	112	41 (23.0%)	71 (26.6%)	
Receptive	49	16 (9.0%)	33 (12.4%)	
Both	284	121 (68.0%)	163 (61.0%)	
Substance use and mental health				
Binge drinking				0.91
Yes	266	107 (59.4%)	159 (58.9%)	
No	184	73 (40.6%)	111 (41.1%)	
Any illicit drug use in past 3 months				0.05
Yes	134	44 (24.7%)	90 (33.5%)	
No	313	134 (75.3%)	179 (66.5%)	
Marijuana				0.19
Yes	128	45 (25.0%)	83 (30.7%)	
No	322	135 (75.0%)	187 (69.3%)	
Stimulants (cocaine, crack, amphetamines)				0.01
Yes	62	16 (8.9%)	46 (17.0%)	

Table 2. (*Continued*)

Participant's characteristics	Total	RJ	SP	Chi-Square
No	388	164 (91.1%)	224 (83.0%)	
Hallucinogens (solvents, LSD, ketamine)				0.45
Yes	38	13 (7.2%)	25 (9.3%)	
No	412	167 (92.8%)	245 (90.7%)	
Tranquilizers				0.44
Yes	30	10 (5.6%)	20 (7.4%)	
No	420	170 (94.4%)	250 (92.6%)	
Erectile dysfunction drugs				0.10
Yes	51	15 (8.3%)	36 (13.3%)	
No	399	165 (91.7%)	234 (86.7%)	
Depression PHQ score				0.62
PHQ-2 score ≥ 3	27	12 (6.7%)	15 (5.6%)	
PHQ-2 score < 3	422	167 (93.3%)	255 (94.4%)	
STD diagnosis				0.87
Yes	89	35 (19.7%)	54 (20.3%)	
No	355	143 (80.3%)	212 (79.7%)	
Active/recent syphilis[2]				0.94
Yes	43	17 (9.6%)	26 (9.8%)	
No	401	161 (90.4%)	240 (90.2%)	
Chlamydia				0.05
Yes	36	9 (5.1%)	27 (10.2%)	
No	408	169 (94.9%)	239 (89.8%)	
Gonorrhoea				0.33
Yes	22	11 (6.2%)	11 (4.1%)	
No	422	167 (93.8%)	255 (95.9%)	
Risk perception				
Number of HIV tests in 12 months prior inclusion				<0.01
0	76	52 (32.7%)	24 (10.4%)	
1–3	235	91 (57.2%)	144 (62.3%)	
>3	79	16 (10.1%)	63 (27.3%)	
PEP in 12 months prior inclusion				0.34
Yes	91	33 (20.9%)	58 (25.0%)	
No	299	125 (79.1%)	174 (75.0%)	
Any GI symptoms[2]				0.01
Yes	178	40 (24.1%)	138 (53.5%)	
No	246	126 (75.9%)	120 (46.5%)	

TGW= Transgender women, STD =Sexually transmitted diseases , RJ= Rio de Janeiro, SP= São Paulo, PHQ= Patient Health Questionnaire, GI= Gastrointestinal. PEP = Post exposure prophylaxis. [1]There was missing information for: Housing situation (n = 7), Sexual role with male (n = 5), Any illicit drug use in last 3 months (n = 3), STDs (n = 6), Number of HIV tests in 12 months prior inclusion (n = 60), PEP in 12 months prior inclusion (n = 60). 5 individuals who reported yellow/indigenous are not included in this table. [2]Socio-demogrphics, except "Housing situation", were assessed at pre-screening visit. Syphilis was assessed at screening visit and GI symptoms, at week 4. All other variables are from enrolment visit. [3]Kruskal-Wallis Test.

model schooling was the strongest predictor of the drug level: participants with ≥12 years had 1.9 times the odds of a higher versus lower drug level than participants with <12 years of schooling. Finally, condomless receptive anal intercourse in the prior 3 months was also associated with higher drug levels (aOR = 1.78; 95% CI: 1.08–2.94).

Overall, 42% (178/424) of the participants reported gastrointestinal symptoms at the week 4 visit. None of these symptoms were associated with drug levels (Figure 2).

Of the 25 enrolled TGW, 15 (60.0%) reported current hormone use, mostly oral and/or intramuscular combined contraceptives (11/15, 73.3%). Notably, only 4 of them

Table 3. Unadjusted and adjusted odds ratios and 95% confidence interval obtained from the ordinal logistic model for the level of TFV-DP according to a set of participant's characteristics aOR = adjusted odds ratio. PrEP Brasil, 2015.

		Level of TFV-DP (%)			Unadjusted		Adjusted	
Characteristic	Total	<2 doses/week *N*(%)	2–3 doses/week *N*(%)	≥4 doses/week *N*(%)	OR (95%CI)	*p*-Value	aOR (95%CI)	*p*-Value
Overall	424	25 (5.9)	66 (15.6)	333 (78.5)	NA	NA	NA	NA
Socio-demographics[1]								
Site location								
RJ	169	16 (9.5)	33 (19.5)	120 (71.0)	1.00	NA	1.00	NA
SP	255	9 (3.5)	33 (12.9)	213 (83.6)	2.12 (1.33–3.78)	<0.01	1.66 (0.97–2.84)	0.06
Age								
18–24 years	106	6 (5.7)	12 (11.3)	88 (83.0)	1.54 (0.8–2.97)	0.20	NA	NA
25–35 years	204	13 (6.4)	32 (15.7)	159 (77.9)	1.12 (0.66–1.92)	0.68	NA	NA
≥35 years	114	6 (5.3)	22 (19.3)	86 (75.4)	1.00	NA	NA	NA
Colour/Race								
White	227	9 (4.0)	30 (13.2)	188 (82.8)	1.00	NA	1.00	NA
Black	54	5 (9.3)	13 (24.1)	36 (66.7)	0.42 (0.22–0.80)	<0.01	0.64 (0.31–1.30)	0.21
Mixed race	138	10 (7.2)	23 (16.7)	105 (76.1)	0.65 (0.39–1.09)	0.10	0.93 (0.53–1.64)	0.81
Schooling								
<12 years	104	10 (9.6)	25 (24.0)	69 (66.4)	1.00	NA	1.00	NA
≥12 years	320	15 (4.7)	41 (12.8)	264 (82.5)	2.37 (1.45–3.88)	<0.01	1.90 (1.10–3.29)	0.02
Gender								
Male	402	23 (5.7)	62 (15.5)	317 (78.8)	1.00	NA	NA	NA
Trans women	22	2 (8.7)	4 (17.4)	17 (73.9)	0.75 (0.27–1.83)	0.55	NA	NA
Housing situation								
Rent or own housing	271	18 (6.6)	43 (15.9)	210 (77.5)	0.77 (0.46–1.27)	0.31	NA	NA
Other (friends/family/public housing)	146	6 (4.1)	21 (14.4)	119 (81.5)	1.00	NA	NA	NA
Steady partner								
Yes	239	17 (7.1)	39 (16.3)	183 (76.6)	0.75 (0.47–1.20)	0.23	NA	NA
No	185	8 (4.3)	27 (14.6)	150 (81.1)	1.00	NA	NA	NA
Sexual behaviour in last 3 months								
Had sex with client								
Yes	22	0 (0.0)	6 (27.3)	16 (72.7)	0.80 (0.30–2.12)	0.65	NA	NA
No	402	25 (6.2)	60 (14.9)	317 (78.9)	1.00	NA	NA	NA

Table3. (*Continued*)

Characteristic	Total	Level of TFV-DP (%) <2 doses/week *N*(%)	2–3 doses/week *N*(%)	≥4 doses/week *N*(%)	Unadjusted OR (95%CI)	*p*-Value	Adjusted aOR (95%CI)	*p*-Value
Condomless receptive anal intercourse								
Yes	191	5 (2.6)	26 (13.6)	160 (83.8)	1.86 (1.14–3.01)	0.01	1.78 (1.08–2.94)	0.02
No	233	20 (8.6)	40 (17.2)	173 (74.2)	1.00	NA	1.00	NA
Sex with HIV-positive partners								
Yes	214	13 (6.1)	35 (16.4)	166 (77.6)	0.83 (0.52–1.34)	0.45	NA	NA
No	197	11 (5.6)	27 (13.7)	159 (80.7)	1.00	NA	NA	NA
Substance use and mental health								
Binge drinking								
Yes	249	16 (6.4)	41 (16.5)	192 (77.1)	0.81 (0.50–1.30)	0.39	NA	NA
No	175	9 (5.1)	25 (14.3)	141 (80.6)	1.00	NA	NA	NA
Any illicit drug use in last 3 months								
Yes	127	3 (2.4)	20 (15.8)	104 (81.9)	1.38 (0.81–2.34)	0.23	NA	NA
No	296	21 (7.1)	46 (15.5)	229 (77.4)	1.00	NA	NA	NA
Depression PHQ score								
PHQ-2 score <3	396	22 (5.5)	60 (15.2)	314 (79.3)	1.00	NA	NA	NA
PHQ-2 score ≥3	27	2 (7.4)	6 (22.2)	19 (70.4)	0.63 (0.27–1.48)	0.29	NA	NA
STD diagnosis[1]								
Yes	79	5 (6.3)	14 (17.7)	60 (76.0)	0.83 (0.46–1.47)	0.51	NA	NA
No	339	19 (5.6)	51 (15.0)	269 (79.4)	1.00	NA	NA	NA
GI symptoms[1]								
Yes	175	9 (5.1)	28 (16.0)	138 (78.9)	1.02 (0.63–1.63)	0.94	NA	NA
No	245	15 (6.1)	37 (15.1)	193 (78.8)	1 .00	NA	NA	NA

aOR = adjusted odds ratio. [1]Socio-demogrphics, except "Housing situation", were assessed at Pre-screening visit. Syphilis was assessed at screening visit and GI symptoms, at week 4. All other variables are from enrollment visit.

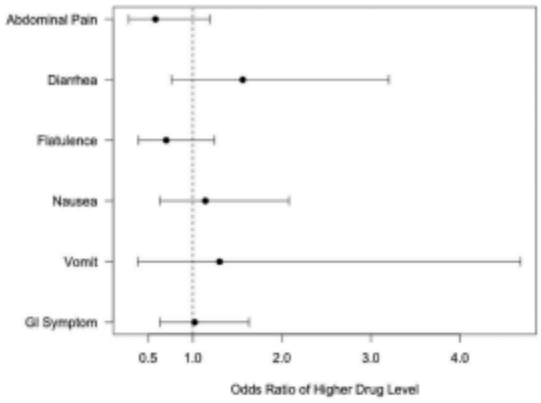

Figure 2. Association of gastrointestinal symptoms and drug level at week-4 after logistic ordinal modelling.

were using regimens in accordance to TGW specific hormone therapy recommendations [29–31]. Logistic and linear unadjusted regression models showed that hormone use was not associated with higher TFV-DP level or with TFV-DP drug concentration.

Discussion

PrEP Brasil is the first demonstration project for PrEP naïve MSM and TGW in Latin America and as such, provides a better approximation of what real-world clinical PrEP delivery might look like in Brazil and perhaps other settings in the region. Our results show that interest in PrEP was high, with 60.9% of PrEP uptake. Moreover, even with limited advertising and no outreach, there were a significant number of self-referrals to the study reflecting demand in the community. Eligible but not enrolled individuals were younger, had lower HIV risk perception (also evidenced by their lower rates of previous HIV testing) and had lower PrEP awareness. Efforts to increase HIV risk perception and PrEP awareness are critically needed, especially among younger MSM, as they currently account for nearly 40% of the AIDS cases in the country, with increases of 41.3% (aged 15–19 years) and 25.1% (aged 20–24 years) observed from 2004 to 2015 [17].

Notwithstanding, 25.1% of the enrolled participants were 18–24 years old, which is higher than in the US PrEP demonstration study and in the San Francisco Kaiser PrEP cohort [26,32]. Enrolment of TGW (5.3%), although small, was higher than reported in other studies [26,32]. This is likely related to the concerted and targeted efforts to provide peer education on PrEP to the TGW community in Rio de Janeiro, where the majority of TGW were enrolled. Such activities can play a major role on expanding access to PrEP for TGW. Moreover, in our study, the majority of enrolled participants were self-referred which is higher than in the US Demonstration project (26). This may be accounted by the different regulatory environment, since PrEP was not available in Brazil during the study timeframe.

The high prevalence (0.4%) of HIV acute infection, which is similar but not quite as high as that reported in the iPrEx study [33], suggests that MSM at high risk for HIV acquisition are interested in PrEP. Indeed, PrEP programs stand as a unique opportunity to identify both individuals with undiagnosed acute/early HIV infection who would benefit from immediate antiretroviral therapy (ART) initiation and at risk for HIV acquisition who would benefit from PrEP. PrEP Brasil participants were younger compared to MSM HIV/AIDS cases reported in RJ and SP, suggesting that MSM enrolled in the study were close to the average age of seroconversion. They were also more educated than the Brazilian general population [34] and the MSM population diagnosed with HIV/AIDS [17] from the same cities. Our results show that roughly 30 and 60% of the enrolled participants reported substance use and binge drinking during the prior 3 months, which is also substantially higher than in the Brazilian general population [35,36]. Likely, heavy alcohol and illicit drug use are major drivers of HIV transmission among MSM in our setting as has been shown to be the case elsewhere [37–41]. Furthermore, the high frequencies of condomless receptive anal sex and STDs among the enrolled participants corroborates that those interested in PrEP are at high risk for HIV acquisition.

The present study used intraerythrocytic drug levels measured in DBS to evaluate TDF-based adherence over a 1–2-month horizon [24]. It is an objective biomarker for cumulative adherence, and we were able to perform this assessment for the vast majority of the enrolled cohort (94.2%). Early adherence (at week 4) has been shown to be highly predictive of PrEP persistence [5,11], highlighting the importance of early assessment and adherence support. At week 4, 94.1% (399/424) participants had DBS TFV-DP concentration in the protective range (consistent with ≥2 pills per week), and for 78% participants DBS TFV-

DP concentrations were in the highly protective range (≥700 fmol/punch, consistent with ≥4 pills per week), which is estimated to provide of 96–100% protection [2,8]. These drug levels are much higher than those from Brazilian participating sites in iPrEx OLE [11]. Higher levels of adherence in demonstration projects when compared to clinical trials are not uncommon and are partially explained by differing motivations to participate in studies. It may also be related to the growing awareness of PrEP effectiveness in the community [18]. These results are reassuring and provide evidence on the feasibility of PrEP implementation in Brazil.

Moreover, as observed in other clinical trials and demonstration projects, drug levels were higher among those at higher risk of HIV acquisition [1,5,42] reinforcing PrEP's likely impact and cost-effectiveness. Notably, in our study population, younger age was not associated with lower drug levels, as opposed to iPrEx OLE findings [11]. Despite the high frequency of GI symptoms reported, results showed they have no association with adherence. Also, in agreement with findings from other PrEP demonstration studies neither illicit substance use or binge drinking were associated with TFV-DP levels [2,5] suggesting that these individuals should not be excluded from receiving PrEP due to concerns about non-adherence.

Over 90% of the enrolled TGW showed protective drug concentration levels, with 72.7% achieving highly protective levels. Of note, drug levels between TGW and MSM were not different (p = 0.47). Drug levels were not different among those using hormones suggesting that drug interactions may not play a major role, but the small sample of TGW may have limited the analysis' power to detect an association between use of hormone and drug levels. TGW represent a smaller population than MSM, and have the highest rates of HIV infection worldwide [15] including in Brazil [14,43]. Yet, few TGW have participated in PrEP studies globally [44]. TGW need immediate access to HIV prevention tools, including PrEP, in order to effectively address their devastating HIV burden. Most importantly, PrEP demonstration studies tailored to this population are urgently needed.

The present study has strengths and limitations that should be acknowledged. A major strength was the assessment of drug levels in almost all participants thus providing robust evidence of early adherence. This measure represents cumulative dosing behaviour rather than only recent dosing behaviour, such as that obtained from plasma testing. The week 4 sampling was prior to attainment of steady-state for TFV-DP, so the levels were used to estimate steady state, for interpretation purposes. PrEP persistence [16] was not evaluated in this study and will be reported later upon study completion. Nevertheless, PrEP Brasil participating sites are referral centres highly motivated and well regarded by the community. As such, the high PrEP uptake and/or adherence observed in PrEP Brasil may not be generalizable to other clinical settings. Moreover, our sample was mostly white and highly educated, not reflecting the general population from the cities where the study was conducted; having said that, it is worth noting that the Brazilian HIV/AIDS epidemic remains mostly restricted to large cities, in particular to the two cities where the study was conducted, suggesting appropriateness of the chosen population. Also, the fact that our sample was not probabilistic may hinder statistical generalizability but do provide strong evidence on the reported associations [45]. Although our study enrolled more TGW than most other demonstration projects, they were underrepresented in the sample and mostly enrolled at one of the participating sites. Finally, the fact that our study was implemented at sites that are part of the Brazilian Unified Health System, where the large majority of the Brazilian population will access PrEP when it becomes available in the country, is another noteworthy strength.

Conclusions

In conclusion, our results show that PrEP for high-risk MSM and TGW can be successfully delivered in the context of the Brazilian Public Health System. The high proportion of participants achieving protective drug levels is encouraging. Moreover, high PrEP early adherence suggests that PrEP use may be an effective strategy to reduce HIV infection among MSM in our setting. Indeed, modelling studies addressing high-risk MSM in high-income settings as well as in Brazil have shown that PrEP is cost-effective in populations at high risk particularly when PrEP efficacy is high [46,47]. Nevertheless, our results suggest that for such benefits to be achieved, strategies to increase risk perception and PrEP awareness among the younger and less educated are needed.

Authors' affiliations
[1]FIOCRUZ, Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil; [2]School of Medicine, Universidade de São Paulo, Brazil; [3]School of Medicine, Universidade de São Paulo, São Paulo, Brazil; [4]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado Denver, Aurora, CO, USA; [5]San Francisco Department of Public Health, Bridge HIV, San Francisco, CA, USA

Competing interests
Dr Liu led trials in which the study drug was donated by Gilead Sciences.

Dr Anderson has received study drug donation, contract work and a research grant from Gilead Sciences, paid to his institution.

Authors' contributions
BG, VGV, BH and RDB conceived the study, interpreted the findings and drafted the manuscript. RIM and ICL performed the statistical analyses with aid from RDB and PML. BG, VGV, BH, PML, RIM, ICL, RDB, AYL, EGK and JVM interpreted the data. EGK, JVM, RV, SG were site investigators and contributed to the study conduct, data collection, interpretation of the results and revised the manuscript. TST and LM contributed to the study conduct, data collection, interpretation of the results and revised the manuscript. PA performed drug-level assessments, contributed to the interpretation of the findings and revised the manuscript. All authors critically revised the article for important intellectual content, read and approved the final manuscript.

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ORCID

Beatriz Grinsztejn http://orcid.org/0000-0003-3692-5155

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4 CONCLUSÕES

1. A maior parte dos HSH e Trans acessados (61,3%) tinha conhecimento sobre PrEP anterior a sua participação no estudo e a grande maioria (82,1%) se interessou em utilizar PrEP se disponível no SUS;

2. A maior parte dos participantes relataram interesse em utilizar outros métodos de prevenção, com exceção da circuncisão. Esse resultado é promissor para a incorporação da PrEP em um contexto da prevenção combinada;

3. A maior parte dos indivíduos elegíveis para PrEP decidiu efetivamente fazer uso dessa medida de prevenção (60,9%);

4. A taxa de adesão precoce foi alta, apesar de 42% terem apresentado sintomas gastrointestinais, referentes a síndrome de início da PrEP. A maior parte dos que decidiram utilizar PrEP apresentaram níveis protetores de droga na semana 4 do estudo (94,1%), com 78% atingido níveis altamente protetores, consistentes com o uso de 4 ou mais comprimidos de TDF/FTC por semana.

5. As práticas sexuais de maior risco para o HIV se mostraram associadas ao interesse em usar PrEP assim como as altas taxas de adesão, apontando para uma alta efetividade da PrEP se direcionada para populações sob maior risco e, consequentemente, para uma relação custo benefício favorável a sua incorporação ao SUS;

6. A importância da escolaridade no contexto da PrEP se evidencia por sua associação com o conhecimento prévio sobre PrEP, a decisão de fazer uso dessa medida e ao nível de adesão a PrEP, com a maior escolaridade sempre associado a melhores resultados;

7. A idade mais jovem se mostrou associada a um menor conhecimento e decisão de não utilizar PrEP mesmo quando elegível para tal, indicando uma maior vulnerabilidade ao HIV desse segmento populacional;

8. A prevalência de doenças sexualmente transmissíveis (20%) foi alta. O mesmo foi visto em relação ao relato de uso de substâncias ilícitas (30%) e o uso abusivo de álcool (60%), que foram superiores a da população em geral, corroborando com a alta vulnerabilidade ao HIV da população acessada.

5 RECOMENDAÇÕES E DESDOBRAMENTOS

1. Nossos resultados apontam para a necessidade de desenvolver estratégias de informação e educação sobre PrEP direcionadas para a população mais jovem e menos educada, na qual a epidemia avança mais rapidamente;

2. A alta prevalência de doenças sexualmente transmissíveis verificada entre os indivíduos que decidiram utilizar PrEP indica que os programs de PrEP podem ser uma ótima oportunidade para diagnóstico e tratamento dessas doenças que, em grande parte são assintomáticas, e que aumentam o risco de aquisição e transmissão do HIV;

3. A alta prevalência do uso de drogas ilícitas e abuso de álcool entre os indivíduos que decidiram utilizar PrEP, indica que programas de PrEP devem estar preparados para identificar esses problemas e ter um sistema de referência para tratamento estabelecido na rede de saúde;

4. Os programas de PrEP oferecem excelente oportunidade para o diagnóstico e tratamento da infecção pelo HIV na sua fase aguda, na qual o potencial de transmissão é maior;

5. O pequeno número de participantes Trans indica a necessidade de desenvolver estratégias para aumentar a participação dessa população em estudos de demonstração, uma vez que, apesar de ser globalmente a população mais afetada pela epidemia de HIV/AIDS, dados sobre a efetividade da PrEP nessa população são praticamente inexistentes;

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Anexo I

Carta de aprovação do CEP do INI/FIOCRUZ

INSTITUTO NACIONAL DE INFECTOLOGIA EVANDRO CHAGAS - INI / FIOCRUZ

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Conhecimento, aceitabilidade e decisão sobre o uso da profilaxia pré-exposição (PrEP) entre homens que fazem sexo com homens (HSH) e mulheres transexuais (TRANS) participantes do Protocolo PrEP Brasil.

Pesquisador: Beatriz Grinsztejn

Área Temática:

Versão: 1

CAAE: 54860116.4.0000.5262

Instituição Proponente: INSTITUTO NACIONAL DE INFECTOLOGIA EVANDRO CHAGAS - INI/FIOCRUZ

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.539.763

Apresentação do Projeto:

A epidemia de HIV no Brasil encontra-se concentrada na população de homens que fazem sexo com homens (14,2%), dado constatado quando compara-se tal valor a população em geral (0,6%). A discrepância desses números faz emergir a necessidade de medidas de prevenção e promoção de saúde para o controle da epidemia. Dados obtidos no estudo iPrEx (Quimioprofilaxia da Prevenção do HIV em HSH e mulheres transexuais) em 2010 demonstraram uma eficácia de 44 % com o uso de antirretrovirais (Truvada®) para prevenção de HIV entre HSH, mulheres transexuais e travestis. A aprovação pelo FDA em 2012 do uso da medicação Truvada® como profilaxia, o consenso do CDC de 2012, que orienta o uso de profilaxia pré-exposição ao HIV e a recomendação da OMS de que os países deveriam desenvolver projetos locais de implementação de PrEP, fundamentaram o desenvolvimento do protocolo PrEP Brasil. O PrEP Brasil é um estudo demonstrativo de Implementação da Profilaxia Pré-Exposição ao HIV para HSH e Mulheres Transexuais (TRANS), conduzido em três centros brasileiros, localizados nas cidades do Rio de Janeiro e São Paulo. Para que o uso da PrEP seja implementado no país, é necessário que o conhecimento, a aceitabilidade, segurança e viabilidade na população-alvo sejam avaliadas. Este presente estudo tem como objetivo descrever o conhecimento, aceitabilidade e a adesão a PrEP entre os voluntários que participaram do Protocolo PrEP Brasil entre as fase de pré-triagem,

Endereço: Avenida Brasil 4365
Bairro: Manguinhos **CEP:** 21.040-360
UF: RJ **Município:** RIO DE JANEIRO
Telefone: (21)3865-9585 **E-mail:** cep@ini.fiocruz.br

triagem, inclusão e semana 4 do estudo. Os objetivos serão alcançados através da análise dos dados coletados nessas visitas e criticados no estudo PrEP Brasil. Na fase de pré-triagem do PrEP Brasil foram entrevistados 1250 HSH e TRANS e 450 foram incluídos no estudo para receber PrEP. Espera-se que os resultados sirvam de subsídio para a implementação do uso de PrEP no Brasil e que sejam publicados na forma de dois artigos científicos em revistas indexadas. Metodologia Proposta: Desenho do Estudo PrEP Brasil (NCT01989611), é um estudo de 48 semanas, multicêntrico, aberto, demonstrativo de PrEP, com o objetivo de avaliar conhecimento, aceitabilidade, segurança e viabilidade de implementar esta nova tecnologia de prevenção no Sistema Único de Saúde do Brasil, para HSH e TRANS com alto risco para aquisição do HIV. O estudo foi conduzido em 3 centros brasileiros: Fundação Oswaldo Cruz (Fiocruz) no Rio de Janeiro, Universidade de São Paulo (USP) e Centro de Referência e Tratamento (CRT), ambos em São Paulo. O presente estudo será realizado utilizando os dados coletados nas visitas de pré-triagem, triagem, inclusão e semana 4 do protocolo PrEP Brasil. Uma amostra de conveniência de 1.254 indivíduos HSH/TRANS foi acessada para a pré-triagem do protocolo PrEP Brasil no período de 01 de abril a 28 de julho de 2015. Destes, 450 indivíduos foram incluídos no estudo para receber PrEP e acompanhados até 01 de setembro de 2015 (semana 4). Critério de Inclusão: Ser HSH ou TRANS, HIV negativo, com alto risco para infecção pelo HIV. Foram considerados critérios de alto risco para aquisição do HIV, neste projeto, qualquer um dos relatos: 1- Sexo anal desprotegido com 2 ou mais parceiros nos últimos 12 meses; 2- Dois ou mais episódios de sexo anal com parceiro sabidamente HIV positivo nos últimos 12 meses; 3- Diagnóstico de DST – sífilis, gonorreia retal ou clamídia retal – nos últimos 12 meses. Critério de Exclusão: 1 - Resultado reagente para HbsAg; 2- Sorologia reagente para o HIV; 3- Clearance de cretinina 60 ml/min ou proteinúria 1 cruz; 4- Qualquer condição médica severa; 5- Uso de antirretrovirais, interferon ou interleucina; 6- Não residir no Estado que o estudo está sendo conduzido ou não ser capaz de fornecer informações para contato. Para conhecimento e aceitabilidade em usar PrEP serão analisadas as porcentagens e modelos de regressão logística serão usados para explorar e quantificar os fatores associados. Variáveis com p-valor < 0.1 na análise bivariada serão incluídos no modelo ajustado inicial. No modelo ajustado final serão incluídas as variáveis que permanecerem no limite de significância de 5% assim como variáveis de confusão, que modificarem o odds ratio de qualquer variável remanescente em mais que 10%. A adesão será analisada a partir dos preditores de níveis de droga que serão acessados usando modelo de regressão logística ordinal. Apenas variáveis estatisticamente significantes a 5% no modelo não ajustado serão incluídos no modelo multivariado. Desfecho Primário: Determinar a medida do conhecimento e aceitabilidade ao uso da

PrEP a partir de níveis percentuais em relação a população acessada na fase da pre triagem do estudo. Descrever as características sociodemográficas e o comportamento sexual da população incluída no estudo e analisar os níveis séricos de tenofovir e entricitabina nos participantes que realizaram a visita da semana 4 do estudo.

Objetivo da Pesquisa:

Avaliar conhecimento e aceitabilidade ao uso de PrEP para prevenção da infecção pelo HIV na população acessada na fase de pré triagem do protocolo PrEP Brasil. Avaliar as características sociodemográficas e comportamento sexual da população incluída no projeto, assim como sua adesão a PrEP, através da dosagem dos níveis séricos de tenofovir e emtricitabina, na visita de semana 4 do Protocolo PrEP Brasil.

Avaliação dos Riscos e Benefícios:

Adequados. Segundo o pesquisador: "Riscos: Não existem riscos previstos para esta análise. Benefícios: Participantes do estudo poderão se beneficiar dos seguintes procedimentos: Aconselhamento sobre redução de riscos FTC/TDF gratuitos para profilaxia pré-exposição por até um ano Acompanhamento clínico e laboratorial gratuitos, incluindo teste de hepatite B. O participante poderá apreciar a oportunidade de contribuir para o conhecimento no campo de prevenção do HIV.".

Comentários e Considerações sobre a Pesquisa:

A pesquisa é extremamente relevante. Os resultados dessa avaliação, como apontado no projeto encaminhado para parecer ético por esse comitê, serão de fundamental importância para o eventual implementação da Profilaxia Pré-Exposição ao HIV para HSH e Mulheres Transexuais (TRANS) no Brasil.

Considerações sobre os Termos de apresentação obrigatória:

Por tratar-se de um estudo com dados secundários, originários de estudo aprovado por este CEP sob CAAE 08405912.9.1001.5262, Estudo PrEP Brasil (NCT01989611), foi apresentado Termo de compromisso e confidencialidade (documento TERMO_DE_COMPROMISSO_confidencialidade_RESPONSABILIDADE.doc), segundo modelo sugerido por esse CEP e pedido de dispensa de TCLE.

Recomendações:

Nenhuma.

Conclusões ou Pendências e Lista de Inadequações:

Por entendermos que nenhuma garantia do participante do estudo foi diminuída em qualquer

parte do protocolo ora avaliado, indicamos a aprovação da condução da pesquisa com a previsão de produção de relatórios anuais (parciais ou final), de acordo com a Res. CNS n.o. 466/12.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_685399.pdf	01/04/2016 11:09:22		Aceito
Projeto Detalhado / Brochura Investigador	Projeto_14_mar_16.docx	01/04/2016 11:08:54	Tânia Krstic	Aceito
Outros	TERMO_DE_COMPROMISSO_confidencialidade_RESPONSABILIDADE.doc	01/04/2016 11:07:09	Tânia Krstic	Aceito
Folha de Rosto	FR_assinada.pdf	01/04/2016 11:06:12	Tânia Krstic	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

RIO DE JANEIRO, 09 de Maio de 2016

Assinado por:
Léa Ferreira Camillo-Coura
(Coordenador)

Drª Léa Ferreira Camillo-Coura
Coordenadora do Comitê de Ética em Pesquisa
Mat. SIAPE 003709620
IPEC / FIOCRUZ

Anexo II

E-mail de confirmação de aceite da publicação do primeiro artigo

Online First: your article is published 2016-08-20

Congratulations

Dear Brenda Hoagland,

We are pleased to inform you that your article has just been published:

Title
Awareness and Willingness to Use Pre-exposure Prophylaxis (PrEP) Among Men Who Have Sex with Men and Transgender Women in Brazil

Journal
AIDS and Behavior, (), 1-10

DOI
10.1007/s10461-016-1516-5

Your article is available as 'Online First':
http://link.springer.com/article/10.1007/s10461-016-1516-5

Anexo III

E-mail de confirmação de aceite da publicação do segundo artigo

Dear Brenda Hoagland,

We are pleased to inform you that your article "High pre-exposure prophylaxis uptake and early adherence among men who have sex with men and transgender women at risk for HIV Infection: the PrEP Brasil demonstration project" is now published in Journal of the International AIDS Society. You can find your article online by following this link:
http://www.jiasociety.org

We remind you that your article is published Open Access and under a Creative Commons License. We encourage you to share this link with colleagues and others who might be interested in reading it. They are welcome to download the PDF and further share it. We thank you for choosing Journal of the International AIDS Society as your publishing outlet and look forward to working with you in the future.

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You will also be able to see a RefBacks section displaying any incoming links from external web sites such as blogs, news sites, or other articles that link directly to your articles. Each RefBack can be edited: it can be ignored, deleted, or published, in which case it appears publicly at the end of your published article on the web site.

Warm regards,
The JIAS Team

Journal of the International AIDS Society
Avenue de France 23 | CH-1202 Geneva | Switzerland
Tel: +41 22 7100 812 | Fax: +41 22 7100 899
Email: editorial@jiasociety.org
Website: http://www.jiasociety.org

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