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LUANA MONTEIRO SPINDOLA MARINS

ADESÃO À PROFILAXIA PRÉ-EXPOSIÇÃO EM HOMENS QUE FAZEM SEXO COM HOMENS (HSH) E MULHERES TRANSEXUAIS EM RISCO DE CONTRAIR HIV

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Para Minha Família: Mãe, Pai, Irmãos, Tios, Avós, Primos, Cristiano e Dona Eliza, meus porto-seguros, fontes de minhas maiores inspirações e felicidade.

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“Ninguém caminha sem aprender a caminhar, sem aprender a fazer o caminho caminhando, refazendo e retocando o sonho pelo qual se pôs a caminhar.”

Paulo Freire

Marins, L.M.S. Rio de Janeiro, 2019. **ADESÃO À PROFILAXIA PRÉ-EXPOSIÇÃO EM HOMENS QUE FAZEM SEXO COM HOMENS (HSH) E MULHERES TRANSEXUAIS EM RISCO DE CONTRAIR HIV.** Tese [Doutorado em Pesquisa Clínica em Doenças Infecciosas] – Instituto de Pesquisa Clínica Evandro Chagas

RESUMO

Introdução: Em uma epidemia concentrada, o HIV se espalha rapidamente em uma ou mais subpopulações específicas, com propagação relativamente modesta na população geral. Na América Latina, algumas populações-chave, como gays, bissexuais e outros homens que fazem sexo com homens (HSH), travestis e mulheres transgêneras (TrMT), são desproporcionalmente afetadas pelo HIV/aids, tendência que está se tornando mais forte nos últimos anos. A Profilaxia Pré-exposição (PrEP) se baseia no uso de medicamentos antirretrovirais (ARV) para a prevenção da aquisição do HIV. O uso diário da combinação oral de entricitabina e tenofovir disoproxil fumarato (FTC/TDF) é eficaz para PrEP, sendo disponível no Sistema Único de Saúde do Brasil (SUS) desde dezembro de 2017. Estudos demonstraram uma forte associação entre os níveis farmacológicos de FTC/TDF no plasma e no interior das células e da proteção contra a aquisição do HIV, atingindo 97-100% de proteção quando os níveis de adesão são alcançados.

Objetivos: Descrever padrões e correlações da adesão à PrEP entre HSH e TrMT de um projeto demonstrativo (PrEP Brasil); avaliar efetividade de mensagens de texto (SMS) na adesão à PrEP; avaliar a adesão autorrelatada da PrEP e suas barreiras e facilitadores.

Primeiro Artigo: Examinar a concordância entre três medidas de adesão indireta (taxa de posse de medicamento ou MPR, contagem de comprimidos e autorrelato) e níveis de medicamento altamente protetores medidos a partir de sangue coletado em papel de filtro (Dried Blood Spots - DBS) entre participantes retidos por 48 semanas no Estudo PrEP Brasil. Os níveis séricos de difosfato de tenofovir (TFV-DP) no DBS foram medidos na semana 48. Áreas sob a curva (AUC) foram usadas para avaliar a concordância entre alcançar níveis protetores de TFV-DP (700fmol/punch) e as medidas de adesão indireta. Os métodos de *Youden Index* e *Distance to Corner* foram empregados para determinar os pontos de corte ideais para cada medida de adesão indireta. Sensibilidade, Especificidade e valores preditivos negativo (VPN) e positivo (VPP) foram calculados para cada ponto de corte encontrado. Finalmente, o teste de Delong foi usado para comparar as AUCs. Todas as medidas de adesão indireta foram capazes de discriminar entre participantes com e sem níveis protetores de TDF-DP (AUC> 0,5). Altos valores de adesão nas três medidas indiretas foram preditivos de níveis protetores (VPP> 0,8), enquanto baixos valores não foram preditivos para a falta de níveis protetores (VPN <0,5). Não foram encontradas diferenças significativas entre os métodos de adesão (p = 0,44).

Segundo Artigo: Avaliar a eficácia do SMS em melhorar a adesão ao uso diário de FTC/TDF durante o estudo PrEP Brasil. Um sub-estudo piloto de SMS interativo foi oferecido a todos os participantes na visita de triagem. Os indivíduos que concordaram em participar foram randomizados 1: 1 para receber apenas o atendimento padrão (SoC), que incluiu aconselhamento de adesão, ou intervenção (SMS). Foram enviados SMS semanalmente aos participantes em um horário pré-determinado. A adesão adequada à PrEP foi definida como tendo MPR ≥ 1,02, que foi o melhor ponto de corte para alcançar níveis protetores de TFV-DP nas semanas 4 e 48. Equações de Estimativas Generalizadas (GEE) foram utilizadas para acessar os fatores associados a adesão adequada à PrEP. Dos 450 participantes incluídos no PrEP Brasil, 417 (92.7%) foram randomizados no sub-estudo: 210 no braço SoC e 207 no braço SMS. Um total de 347 (83.2%) participantes completaram o estudo, e receber SMS não aumentou a retenção na semana 48. Uma maior proporção de participantes no grupo recebendo SMS apresentou adesão adequada à PrEP ao longo do estudo. Em análise multivariada, receber SMS foi preditor de adesão adequada à PrEP (AOR = 1,37; IC 95%: 1,07-1,75) quando ajustado

por visita, localidade, idade sexo anal receptivo sem preservativo e uso de álcool.
Terceiro Artigo: Avaliar a adesão autorrelatada à PrEP (recordatório de 30 dias) e as barreiras e facilitadores percebidos entre os retidos por 48 semanas no estudo da PrEP Brasil. A regressão logística foi utilizada para avaliar os preditores da adesão ótima (= 100%). A mediana de adesão nos últimos 30 dias foi de 100% (IQR: 92-100); 60,6% dos participantes (205/338) relataram adesão ótima. A maioria (82,2%; 278/338) dos participantes relatou não ter dificuldade em tomar FTC / TDF e 81,3% (274/338) relataram capacidade excelente ou muito boa. Barreiras e facilitadores percebidos foram relatados por 38,2% (129/338) e 98,5% (333/338), respectivamente; os principais facilitadores do uso da PrEP incluíram a associação com alguma atividade diária (59%), envolvimento com a PrEP (49%), manter os comprimidos em algum lugar visível e transportar a medicação com eles (45%), uso de alarme (39%) e medo de se infectar pelo HIV (38%). As principais barreiras para a PrEP incluíram a esquecimento de doses (50%), mudança na rotina diária (38%), falta de pílulas (25%) e ausência da pílula no momento da dose (12%). Dificuldades relatadas devido ao uso de drogas ou álcool, nenhum risco percebido, questões de privacidade ou efeitos colaterais foram incomuns (≤ 10%). Na análise multivariada, ser do Rio de Janeiro, TrMT, o uso de estimulantes e ter percepção de barreiras à PrEP foram associados à diminuição da chance de adesão ótima.
Conclusões: Altos níveis de adesão mensurados por diferentes métodos indiretos (contagem de comprimidos, MPR e autorrelato) foram verificados na semana 48 e todos os métodos foram capazes de discriminar participantes que atingiram ou não níveis protetores de tenofovir. A intervenção por SMS foi eficaz para melhorar a adesão e a cobertura de PrEP ao longo do estudo, mas não teve impacto na retenção na semana 48. Nossos achados fornecem informações para elaboração, reforço e atualização de estratégias para melhorar a adesão, e para desenvolver as melhores práticas para promover a adesão à PrEP em nosso contexto.

Palavras-chave: PrEP, Adesão à PrEP, Facilitadores do uso da PrEP, Barreiras ao uso da PrEP, Prevenção do HIV, América Latina, Detecção de Drogas, SMS

Marins, L.M.S. Rio de Janeiro, 2019. **ADHERENCE TO PRE-EXPOSURE PROPHYLAXIS IN MEN WHO HAVE SEX WITH MEN (HSH) AND TRANSEXUAL WOMEN AT RISK OF HIV INFECTION.** Tese [Doutorado em Pesquisa Clínica em Doenças Infecciosas] – Instituto de Pesquisa Clínica Evandro Chagas

Background: In a concentrated epidemic, HIV spreads rapidly in one or more specific subpopulations, with relatively modest spread in the general population. In Latin America, some key population such as gays, bisexuals and other men who have sex with men (MSM) and transgender women (TGW) are disproportionately affected by HIV/AIDS, a trend that is becoming stronger in recent years. Pree-exposure Prophylaxis (PrEP) is based on the use of antiretroviral (ARV) drugs to prevent HIV acquisition. The daily oral use of emtricitabine and tenofovir disoproxil fumarate (FTC/TDF) is effective for PrEP and has been available in the Brazilian Public Health System (SUS) since December 2017. Studies have demonstrated a strong association between pharmacological levels of FTC/TDF in plasma or inside the cells and protection against HIV acquisition, achieving 97-100% protection when levels of adherence are achieved.

Objectives: To describe patterns and correlations of adherence to PrEP among MSM and TGW in a demonstration project (PrEP Brasil); evaluate the effectiveness of text messages (SMS) in adherence to PrEP; evaluate self-reported adherence to PrEP and its perceived barriers and facilitators.

First Manuscript: To evaluate the concordance between three indirect adherence measures (medication possession ratio or MPR, pill count and self-report) and highly protective drug levels measured by dried blood spot (DBS) among participants retained through 48 weeks in the PrEP Brasil Study. Tenofovir diphosphate (TFV-DP) concentration in DBS was measured at week 48. Areas under the curve (AUC) were used to evaluate the concordance between achieving protective levels of TFV-DP (≥700fmol/punch) and the indirect adherence measures. Youden's index and distance to corner were used to determine the optimal cutoff points for each indirect adherence measure. Sensitivity, specificity, negative (NPV) and positive (PPV) predictive values were calculated for the each cutoff points. Finally, Delong test was used to compare AUCs. All indirect adherence measures discriminated between participants with and without protective drug levels (AUC>0.5). High adherence was predictive of protective levels (PPV>0.8) while low adherence was not predictive of lack of protective levels (NPV<0.5). No significant differences were found among the adherence methods (p=0.44).

Second Manuscript: To evaluate the effectiveness of SMS in improving adherence to daily FTC/TDF use during the PrEP Brasil study. An interactive SMS pilot sub-study was offered to all participants on the screening visit. Subjects who agreed to participate were randomized 1: 1 to receive only standard care (SoC), which included adherence counseling, or intervention (SMS). SMS was sent weekly to participants at a predetermined time. Adequate adherence to PrEP was defined as having MPR ≥ 1.02, which was the best cutoff point for reaching protective levels of TFV-DP at weeks 4 and 48. Generalized Estimation Equations (GEE) were used to access factors associated with adequate adherence to PrEP. Of the 450 participants included in PrEP Brasil, 417 (92.7%) were randomized in the sub-study: 210 in the SoC arm and 207 in the SMS arm. A total of 347 (83.2%) participants completed the study, and receiving SMS did not increase retention at week 48. A higher proportion of participants in the group receiving SMS showed adequate adherence to PrEP throughout the study. In multivariate analysis, receiving SMS was a predictor of adequate adherence to PrEP (AOR = 1.37; 95% CI: 1.07-1.75) when adjusted for visit, location, age, receptive anal sex without condom and alcohol use.

Third Manuscript: To evaluate self-reported PrEP adherence (30-days recall) and its perceived barriers and facilitators among participants retained through 48 weeks in the PrEP Brasil study. Logistic regression was used to evaluate predictors for optimal adherence (=100%). Median adherence in the past 30-days was 100%(IQR:92-100); 60.6% participants (205/338) reported optimal adherence. Most (82.2%; 278/338) reported not having difficulty

with taking FTC/TDF and 81.3% (274/338) reported excellent or very good ability. Perceived barriers and facilitators were reported by 38.2%(129/338) and 98.5%(333/338), respectively; main facilitators to PrEP use included associating with some daily activity (59%), being engaged with PrEP (49%), keeping the tablets in some visible place and carrying the medication with them (45%), use of alarm (39%), fear of becoming HIV infected (38%). The main barriers to PrEP use included forgetting doses (50%), change in daily rotine (38%), pills shortage (25%) and not having the pill at time of dose (12%). Reported difficulties due to drug or alcohol use, no HIV perceived risk, privacy issues or side effects were uncommon (≤10%). In multivariate analysis, being from Rio de Janeiro, TGW, stimulant use and having perceived barriers to PrEP use were associated with decreased odds of optimal adherence.
Conclusions: High adherence levels measured by different indirect methods (pill count, MPR and self-report) were verified at week 48 and all methods were able to discriminate participants who achieved or not protective levels of tenofovir. The SMS intervention was effective in improving adherence and PrEP coverage throughout the study, but had no impact on retention at week 48. Our findings provide information for designing, reinforcing, and updating strategies for improving adherence, and for developing best practices for promoting adherence to PrEP in our context.

Key words: PrEP, PrEP Adherence, Facilitators to PrEP use, Barriers to PrEP use, HIV prevention, Latin America, drug detection, SMS.

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LISTA DE ABREVIATURAS e SIGLAS

ARV: Medicamentos antirretrovirais

CONITEC: Comissão Nacional de Incorporação de Tecnologias no SUS

DBS: Dry blood spots (sangue coletado em cartões de papel de filtro)

DST: Doenças Sexualmente Transmissíveis

FTC/TDF: entricitabina 200mg/tenofovir diproxil fumarato 300mg

FTC: Entricitabina

HSH: Homens que fazem sexo com homens

IMB: Informação, motivação e habilidades comportamentais (do inglês, Information – Motivation - Behavioral Skills)

iNSC: Next step couseling

iPrEx: Iniciativa de Profilaxia Pré-Exposição

mHealth: Mobile health

MPR : Taxa de posse de medicamentos (Medication Possetion Ratio)

OMS: Organização Mundial de Saúde

PBMC: Células mononucleares do sangue periférico

PC: Contabilidade de comprimidos (Pill Count)

PEP: Profilaxia pós-exposição

PrEP: Profilaxia pré-exposição

PVHA: Pessoas vivendo com HIV/AIDS

RBCs: Glóbulos vermelhos

SMS: Mensagem de Texto (do inglês, Short Message Service)

SR: Autorrelato (Self-report)

TAR: Terapia antirretroviral

TDF: Tenofovir diproxil fumarato

TFV: Tenofovir

TFV-DP: Tenofovir difosfato

TrMT: Travestis e mulheres transexuais

UDI: Usuários de drogas injetáveis

UNAIDS: Joint United Nations Programme on HIV and AIDS

WHO: Who world health organization (OMS)

SUMÁRIO

1. INTRODUÇÃO

1.1. EPIDEMIOLOGIA DA INFECÇÃO PELO HIV ENTRE GAYS, BISEXUAIS E OUTROS HOMENS QUE FAZEM SEXO COM HOMENS (HSH), TRAVESTIS E MULHERES TRANSEXUAIS (TRMT)

O HIV/AIDS é uma das maiores pandemias já enfrentada pela humanidade. Estima-se que no final de 2016, existiam cerca de 36,9 milhões de pessoas vivendo com HIV (PVHA) (1).

A epidemia global de HIV/AIDS foi reconhecida primeiramente entre gays, bissexuais e outros homens que fazem sexo com homens (HSH) no início dos anos 80 e, desde então, esse grupo se mantém entre os mais vulneráveis para a aquisição da infecção pelo HIV, sendo uma das populações com maior incidência de HIV (2), a despeito da expansão global das intervenções no tratamento e na prevenção da infecção pelo HIV. Dados sugerem que o risco de aquisição do HIV entre HSH em 2017 foi 28 vezes maior do que entre homens heterossexuais (3). Estudos demonstram que HSH e travestis e mulheres transexuais (TrMT) são respectivamente 19 e 50 vezes mais propensos a se infectar que a população adulta em geral (4). Segundo a Joint United Nations Programme on HIV and AIDS (UNAIDS), em 2017, HSH representaram 57% das novas infecções por HIV na Europa Ocidental e Central e América do Norte ; 41% das novas infecções na América Latina; mais de 25% das novas infecções na Ásia, Pacífico e Caribe; cerca de 20% das novas infecções na Europa Oriental, Ásia Central, no Oriente Médio e norte da África, e estima-se que 12% das novas infecções na África ocidental e central (3). Uma meta-análise dos dados sobre TrMT em países de baixa e média renda indicou uma prevalência de HIV de 17,7% (IC 95% de 15,6 a 19,8). A razão de probabilidade de infecção pelo HIV entre as TrMT, em comparação a todos os adultos de 15 a 49 anos, nestes países foi de 50,0 (IC 95% de 26, 5 a 94,3) e 46,3 (IC 95% de 30,3 a 70,7) em comparação a homens (5).

Estima-se que 47% das novas infecções por HIV em todo o mundo em 2017 foram entre populações-chave e seus parceiros sexuais (3). Apesar da clara necessidade de intervenção, os recursos para programas de prevenção e tratamento do HIV nessas populações continuam escassos (3,6,7). Segundo Arreola (2014), estima-se que menos de 2% do financiamento global de prevenção do HIV seja voltado para os HSH e que os serviços de prevenção só atingem 10% dos HSH em todo mundo, não sendo suficientes para as necessidades dessa população (8).

O Brasil, com uma população de aproximadamente 210 milhões (9), ocupa o segundo lugar nas Américas em número de casos de AIDS notificados. Desde o início da epidemia de aids no Brasil até junho de 2018, foram notificados ao Ministério da Saúde (MS) do Brasil 926.742 casos de aids (10). Após mais de 30 anos, o Brasil apresenta uma epidemia estável e concentrada em subgrupos com maior vulnerabilidade. No período de 2007 a junho de 2018, foram notificados

um total de 169.932 (68,6%) casos de infecção pelo HIV em homens e 77.812 (31,4%) casos em mulheres. Entre os homens acima de 13 anos, 59,4% dos casos de infecção pelo HIV foram decorrentes de exposição homossexual ou bissexual; 36,9% por exposição heterossexual, e 2,6% foram entre usuários de drogas injetáveis (UDI) (10). Nos grupos populacionais em situação de maior vulnerabilidade, as taxas de prevalência de HIV encontradas em estudos realizados pelo Departamento de DST, Aids e Hepatites Virais em 2016 foi de 19,8% entre HSH com 25 anos ou mais de idade e de 9,4% entre os HSH de 18 a 24 anos; 5,3% entre as profissionais do sexo. A prevalência de HIV dentre os usuários de drogas injetáveis (UDI) no Brasil vem diminuindo ao longo dos anos, representando 3,2% dos casos entre homens e 1,9% dos casos entre mulheres no ano de 2016 (11).

Um estudo comparou características descritivas do comportamento social em duas Pesquisas Nacionais de Vigilância Biológica e Comportamental (BBSS) do HIV realizados em 2009 e 2016 entre HSH no Brasil. Em 2009 e 2016, 3749 e 4176 HSH foram recrutados usando amostragem dirigida pelo entrevistado (RDS, do inglês Respondent Driven Sampling), respectivamente. Neste período, a prevalência de HIV entre HSH aumentou de 12,1% para 18,4% (12). Os resultados desse estudo indicaram uma tendência de comportamento de risco entre HSH brasileiros, especialmente entre os mais jovens, com um aumento nas práticas de risco de 2009 para 2016 (relações sexuais com múltiplos parceiros, não uso de preservativos tanto em sexo anal insertivo quanto receptivo), níveis mais baixos de aconselhamento e conhecimento sobre informações sobre HIV e aumento do uso de drogas ilícitas. Segundo os autores, esses resultados são preocupantes podendo resultar em um potencial aumento na prevalência de HIV e outras IST entre HSH no Brasil (13). A segunda Pesquisa Nacional, realizada em 2016, também avaliou a prevalência de infecção pelo HIV entre os respondentes (90.2% foram testados para HIV), demonstrando um aumento na prevalência de 2009.

Um outro estudo usando a metodologia RDS, estimou a prevalência de HIV entre TrTM e os fatores associados com infecções recém-diagnosticadas no Rio de Janeiro. Este estudo demonstrou uma alta prevalência de HIV entre TrMT no Rio de Janeiro (31,2% IC95% 18,8–43.6), o que corresponde a uma prevalência maior que em qualquer outra população chave na epidemia brasileira de HIV (14).

1.2. PREVENÇÃO DA INFECÇÃO PELO HIV

A qualidade e o acesso aos serviços de prevenção da infecção pelo HIV têm geralmente melhorado, e uma variedade crescente de intervenções eficazes no combate a infecção está

disponível. As estratégias comportamentais de prevenção do HIV se concentram na redução das práticas de alto risco, incluindo a prática sexual desprotegida e compartilhamento de agulhas contaminadas, entre outros (15).

Adicionalmente à abordagens comportamentais, diversas intervenções biomédicas estão sendo implementadas, como por exemplo, o início da terapia antiretroviral (TAR) independentemente da contagem de células CD4, bem como a circuncisão masculina voluntária e o uso de medicamentos antirretrovirais (ARV), tanto para profilaxia pré-exposição (PrEP) quanto pós-exposição (PEP) (4) De modo geral, a prevenção combinada tem se tornado a abordagem preferida na prevenção da infecção pelo HIV (15).

A prevenção biomédica da infecção pelo HIV engloba um leque diversificado de estratégias em estágios diferentes de desenvolvimento, incluindo: (a) uso de microbicidas retais e vaginais; (b) PrEP; (c) PEP; (d) vacinação; (e) circuncisão masculina; (f) testagem, vínculo e retenção nos serviços de saúde ("test-and-treat"); e (g) adesão reforçada entre as pessoas vivendo com HIV/AIDS (PVHA), tratamento como prevenção (15).

Os pacotes de prevenção combinada podem consistir em diferentes componentes - como aconselhamento e testagem expandidos, intervenções de promoção de comportamento mais seguro, expansão dos serviços do tratamento de pacientes infectados pelo HIV, e intervenções especiais direcionadas aos grupos de risco. Dentre as diferentes abordagens, a testagem, o tratamento precoce e medidas biomédicas de prevenção tem recebido crescente importância na prevenção e tratamento do HIV.

1.3.PROFILAXIA PRÉ-EXPOSIÇÃO

A profilaxia Pré-exposição (PrEP) se refere ao uso de ARVs para reduzir o risco de infecção por pessoas com sorologia negativa para o HIV (16,17).

O desenvolvimento da PrEP começou no início da década passada (18). A primeira evidência da sua eficácia foi vista em 2010, no estudo Caprisa 004, para o gel vaginal de tenofovir entre as mulheres idade 18-40 anos na África do Sul, demonstrando 39% de eficácia (IC95% 6-60%; p-valor: 0,017)(19).

A eficácia da PrEP em pessoas em alto risco de contrair HIV tem sido demonstrada em diversos estudos (20–25). Estudos realizados com HSH e TrMT mostraram que pessoas que receberam PrEP tinham menor probabilidade de se infectar com o HIV do que aqueles que não a receberam. O estudo iPrEx (Iniciativa de Profilaxia Pré-Exposição), foi um estudo randomizado controlado por placebo que demonstrou uma redução de 44% na incidência entre HSH que

receberam uma dose diária da combinação de antirretrovirais entricitabina 200mg e tenofovir diproxil fumarato 300mg (FTC/TDF)(20). Dentre os voluntários com maior adesão à profilaxia, houve menor número de infecções, com redução de 73% na incidência de infecções (20,26), tendo sido demonstrada 90% de eficácia entre aqueles com níveis sanguíneos detectáveis do medicamento (16,20,27), indicando a importância da adesão ao uso do medicamento para a profilaxia.

O estudo randomizado "Partners in a PrEP", incluiu 4.758 casais sorodiscordantes para o HIV no Quênia e em Uganda, demonstrando uma redução de 67% (IC 95% 44–81, p < 0, 001) na incidência na infecção pelo HIV entre os parceiros que fizeram uma dose diária de TDF e uma redução de 75% (IC 95% 55–87, p < 0,001) na incidência na infecção pelo HIV entre os parceiros que fizeram uma dose diária de TDF/FTC(28).

O estudo randomizado TDF2 de PrEP entre homens e mulheres heterossexuais, incluiu 1219 homens e mulheres não infectados pelo HIV e demonstrou que uma dose única diária de FTC/TDF reduziu em 62% a incidência de infecção por HIV nesta população (IC 95%, 21, 5 a 83,4; p= 0.03) (16,24). Por outro lado, os estudos FEM-PrEP e VOICE, que recrutaram mulheres cisgêneras na África, não foram capazes de demonstrar nenhum efeito (18,29,30). Isto foi explicado, principalmente, pelos baixos níveis de adesão ao regime de prevenção recomendada (18,29,30).

As evidências demonstradas no estudo iPrEx (20), Partners PrEP (28) e TDF2 trial (31) subsidiaram a aprovação do uso de FTC/TDF para a prevenção da transmissão sexual do HIV pelo FDA (US Food and Drug Administration) em julho 2012 (32,33). Em maio de 2014, o CDC (Centers for Disease Control and Prevention) publicou as diretrizes de prática clínica de PrEP (27).

O estudo PROUD, conduzido na Inglaterra, acompanhou 544 HSH com sorologia negativa para o HIV e que relataram sexo desprotegido dentro de 90 dias antes da inclusão no estudo. Os participantes foram randomizados para receber FTC/TDF imediatamente ou após 12 meses (braço adiado). O estudo demonstrou uma alta proteção dos voluntários em uso do FTC/TDF, com um decréscimo de 86% no risco de infecção (86%, IC90% 64-96) e uma alta incidência de infecção dos voluntários no braço adiado (22,34,35). Em 2014, com a demonstração de que o uso de PrEP foi altamente protetora para HSH com alto risco de infecção, o DSMB (Data and Safety Monitoring Board) do estudo recomendou que a PrEP fosse oferecida a todos os participantes. Os resultados do estudo PROUD foram fundamentais para a introdução da PrEP ao pacote de prevenção combinada para HSH em risco de infecção por HIV (22).

No estudo randomizado IPERGAY, conduzido na França e Canadá, 400 HSH com alto

risco de contrair HIV foram randomizados para receber FTC/TDF ou placebo. Os voluntários utilizaram PrEP sob demanda antes de uma relação sexual desprotegida programada (dois comprimidos entre 2-24h antes da relação sexual) e depois utilizar um comprimido diário do medicamento pelos dois dias subsequentes. Os resultados preliminares do estudo demonstraram uma eficácia de proteção de 86% (IC 95%, 40 a 98; p= 0.02) no braço de FTC/TDF (23,34,35). Os resultados da fase aberta do estudo demonstraram uma eficácia de 97% (IC95% 81-100). O estudo IPERGAY, ao demonstrar que a PrEP oral sob demanda ou Event-driven PrEP (ED-PrEP) é altamente efetiva nessa população, forneceu uma alternativa a PrEP oral diária, expandindo as opções para prevenção do HIV (36).

Atualmente a PrEP está disponível em vários países, incluindo o Brasil, onde desde dezembro de 2017 tem sido oferecida como uma política de saúde pública para populações em alto risco de contrair HIV, como HSH e TrMT (37). O Brasil é pioneiro na América Latina em políticas públicas para tratamento e prevenção do HIV/AIDS (38), com acesso gratuito e universal a antirretrovirais e programas de prevenção com intervenções centradas em intervenções estruturais e comportamentais (39). Acompanhando as evidências acumuladas da eficácia da PrEP, desde 2013, o Ministério da Saúde Brasileiro (MS) financia projetos visando acessar a aceitabilidade e viabilidade da implementação de PrEP no país, com o objetivo de gerar evidências para a construção de uma política nacional de PrEP(40), quais podemos citar o estudo PrEP Brasil (41); o Projeto Combina; o Estudo PrEParadas; o Projeto Horizonte; Projeto para mulheres trans da Universidade Federal da Bahia (Salvador) e ImPrEP (42). A demanda de PrEP no Brasil foi avaliada por Luz e cols (43), sendo estimada em 66.000 – 98.000 de brasileiros HSH com idade entre 15-64 anos. De janeiro a setembro de 2018, 5.712 indivíduos iniciaram PrEP fornecido pelo Sistema Único de Saúde (SUS) (44).

1.4.ADESÃO À PREP

Como demonstrado anteriormente, os resultados de quatro ensaios clínicos randomizados (CAPRISA 004, iPrEx, TDF2, e Partners on PrEP) forneceram evidências claras da proteção da infecção pelo HIV pela PrEP, com estimativas de eficácia entre 39% -75% nas comparações por intenção de tratar e entre 90% -92% entre aqueles que tiveram níveis detectáveis no sangue do medicamento do estudo (45).

Da mesma forma, a falta de eficácia em dois ensaios (FEM-PrEP e VOICE) indicam que a adesão é um fator importante para a eficácia da PrEP (18,29,30). No estudo FEM-PrEP, por exemplo, as avaliações de acompanhamento demonstraram que a adesão no estudo foi muito baixa (<40%) para avaliar a eficácia do FTC/TDF nessa população. O estudo foi interrompido em abril

de 2011 devido à falta de eficácia (29,46,47).

O estudo VOICE foi um estudo randomizado controlado por placebo para avaliar o uso diário de TDF oral, FTC/TDF oral ou tenofovir (TFV) 1% gel vaginal para PrEP em mulheres na África do Sul, Uganda e Zimbábue. Em 2011, o comitê de monitoramento de dados e segurança recomendou que o braço de TDF por via oral fosse suspenso e posteriormente o mesmo ocorreu em relação ao gel TFV. Foi recomendado que os grupos FTC/TDF e placebo oral continuassem até o final do estudo. Nesse estudo a adesão diária aos produtos investigacionais (formulações orais ou vaginais) foi baixa e nenhum regime reduziu significativamente o risco de aquisição do HIV(30).

Neste sentido, a adesão é um componente crítico para a efetividade da PrEP, maximizando o impacto desta estratégia de prevenção na saúde pública (48,49). Portanto, a monitoração da adesão ente indivíduos incluídos em programas de PrEP é de grande importância no cenário clínico. No entanto, uma avaliação precisa da adesão é um desafio. Os métodos existentes para avaliar a adesão são limitados por várias razões que foram bem descritas na literatura (50–54), cada medida tendo suas vantagens e desvantagens (53,54), não havendo padrão de ouro para sua medição (51,55).

1.4.1. Medidas de Adesão a PrEP

Níveis séricos de Tenofovir Difosfato (TFV-DP)

Os níveis de concentração de medicamentos poderiam ser considerados a medida mais precisa para quantificar a adesão, mas os altos custos das metodologias disponíveis inviabilizam a implementação na prática clínica, especialmente em um contexto de saúde pública (55).

O TDF é um pró-fármaco oral do antirretroviral análogo de nucleotídeo TFV. Uma vez absorvido, o TDF é convertido em TFV que por sua vez é metabolizado em tenofovir difosfato (TFV-DP) intracelularmente (56,57).

Um estudo de modelagem farmacocinética demonstrou a relação entre o uso da PrEP e sua eficácia, mostrando que a adesão é essencial para maximizar a eficácia da PrEP (50,58,59). O nível de TFV-DP é uma evidência objetiva do uso de comprimidos e pode ser entendido como a medida mais precisa para quantificar a adesão se comparada com as outras medidas de adesão indireta (contagem de comprimidos, posse de medicamento e autorrelato).

O estudo iPrEX (20) mediu os níveis de TFV-DP nas células mononucleares do sangue periférico (PBMCs) e no plasma. As concentrações de TFV-DP não se acumulam no plasma significativamente ao longo do tempo (meia-vidas plasmáticas é de 17 horas) e, portanto, não

podem ser usadas para diferenciar entre doses únicas, intermitentes e consistentes, mas podem ser usadas como medidas de adesão a curto prazo (60). O TFV-DP no PBMC, por sua vez, tem meia-vida de 6,25 dias e espera-se que detecte o TFV-DP após 14 dias após última dose de FTC/TDF. Dessa forma, o acúmulo de TFV-DP no PBMC tem sido considerado uma melhor medida de adesão se comparado ao acúmulo no plasma (20). No entanto, o processo de isolar PBMCs é caro, complexo e inviável em muitos cenários (60).

Uma alternativa ao uso de plama e PBMC é o uso de sangue coletado em cartões de papel de filtro (dry blood spots - DBS) para avaliar os níveis de ARV nos glóbulos vermelhos (RBCs) (61). Os níveis de TFV-DF no DBS têm uma meia-vida longa de 17 dias e alto acúmulo representando o grau de exposição ao fármaco ao longo do tempo o que proporciona a avaliação do uso de FTC/TDF médio de 1 a 3 meses (57). Em outras palavras, a principal limitação deste método é que essa medida de adesão nos dá a informação de uma adesão média ao longo do tempo e não pode discriminar os padrões de uso da PrEP (57,62,63). Por exemplo, os níveis protetores de TFV-DP podem ser alcançados mesmo se um indivíduo apresentar períodos de alta adesão alternando com períodos de interrupção de PrEP em um determinado período.

Resultados do estudo iPrEX Open-label (iPrEX OLE) demonstraram a seguinte correspondência de doses tomadas por semana com a concentração de TFV-DP e os níveis de proteção (**Tabela 1, Figura 1**) (59,64).

Tabela 1. Relação entre concentração de TFV-DP, doses semanais e níveis de proteção

Concentração de TVF-DP (fmol/punch)	**Uso de PrEP**	**Proteção**
< 350 fmol/punch	< 2 doses semanais	**Sem Proteção**
≥ 350-699 fmol/punch	2-3 doses semanais	86% (IC 95% 21% a 99%) **Níveis Protetores**
≥ 700 fmol/punch	**≥4 doses semanais – (Alta Adesão)**	100% (IC 95% 86% a 100%) **Níveis Altamente Protetores**

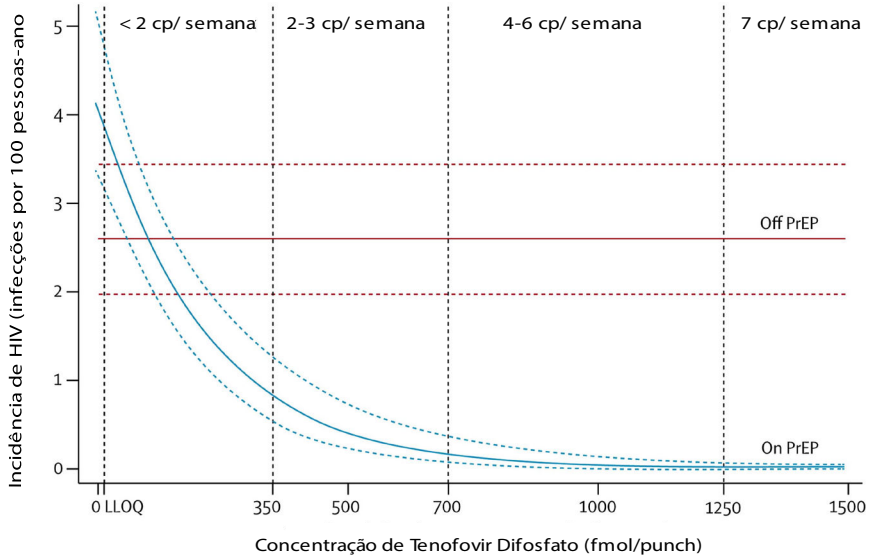

Figura 1. Profilaxia pré-exposição e incidência de HIV (adaptado de Grant et al 2014) **(59)**

Autorrelato (Self-report, SR)

Autorrelato é a medida de adesão mais comum na prática clínica (65). As vantagens dessa medida são a facilidade de coleta, baixo custo e o fato de que relatos de não-adesão tenderem a ser precisa (53). Por outro lado, sua precisão depende da memória ou do conforto dos participantes ao fornecer informações "verdadeiras" (66), assim, essa medida está sujeita a viés (viés de lembrança e de "desejabilidade social"), o que muitas vezes levam à superestimação da adesão. Uma forma de melhorar a adesão ao autorrelato é proporcionar um ambiente em que o indivíduo se sinta livre e confiante para relatar comportamento socialmente indesejado. (53).

Contabilidade de comprimidos (Pill Count, PC)

A contabilidade de comprimidos é uma medida de adesão mais objetiva (se comparada com o autorrelato) que pode melhorar a precisão do monitoramento da adesão. Esta medida também é fácil de ser coletada e relativamente barata (53). Por outro lado, este método está sujeito a várias limitações, como ser demorado e manipulação (por exemplo, comprimidos descartados, perdidos ou dados) e pode não refletir o real uso da PrEP (54,67).

Levando em consideração o uso diário de 1 comprimido de FTC/TDF, a contabilidade de comprimidos é obtida pelo número de comprimidos dispensados na visita anterior menos o número de comprimidos devolvidos na visita em questão, dividido pelo número de dias entre as duas visitas. Os valores são dados em porcentagem.

$$PC = 100\ X\ \frac{\#comprimidos\ dispensados - \#comprimidos\ retornados}{\#dias\ entre\ as\ visitas}$$

Taxa de posse de medicamentos (Medication Possetion Ratio – MPR)

A taxa de posse de medicamentos (Medication Possetion Ratio – MPR) representa o reabastecimento da farmácia e é obtido através de registros de dispensação. O MPR corresponde à porcentagem de dias em que os pacientes estão em posse de seus medicamentos (68) refletindo a cobertura da pílula ao longo do tempo. Da mesma forma que a contagem de comprimidos, o MPR não reflete necessariamente o uso de PrEP, pois indica dispensação de farmácia e não a ingestão de drogas. Por exemplo, MPR acima de 1,0 não significa excesso de adesão, mas indica que o indivíduo possui a medicamento suficiente para suprir um determinado tempo de uso de PrEP, o que é necessário para o uso adequado. De acordo com a "WHO consultation on PrEP adherence - Consulta da sobre a adesão à PrEP da OMS", o reabastecimento da farmácia "pode ser interpretado como uma adesão máxima prevista à PrEP"(63)

Da mesma forma, considerando o uso diário de 1 comprimido de FTC/TDF por dia, MPR é calculado pela razão entre o número de comprimidos dispensados na visita anterior e o número de dias decorridos entre as visitas.

$$MPR = \frac{\#comprimidos\ dispensados}{\#dias\ entre\ as\ visitas}$$

1.4.2. Estratégias para promoção da adesão

Dentre os diversos modelos utilizados na promoção de adesão no contexto da infecção pelo HIV, as abordagens cognitivo-comportamentais têm se destacado. Essa abordagem, leva em consideração a relação entre as variáveis psicológicas (percepção de controle, otimismo, auto-eficácia, habilidades de enfrentamento do estresse, crenças de saúde e atitudes relacionadas à doença e ao tratamento) e o comportamento de adesão e não apenas um aspecto isolado. Dentre as abordagens cognitivo-comportamentais existentes, pode-se destacar o modelo IMB (do inglês, Information – Motivation - Behavioral Skills), composto por três determinantes - informação, motivação e habilidades comportamentais - como pré-requisitos do uso consistente e correto da terapia e fornece orientação para a concepção, implementação e avaliação de estratégias de promoção da adesão à TAR (69), (70).

Uma adaptação do modelo IMB para adesão à PrEP, denominada next step couseling (iNSC), foi desenvolvida para o estudo iPrEX. O iNSC é uma discussão baseada em pontos fortes,

com foco na identificação de proteção da saúde sexual, necessidades de adesão a PrEP e estratégias sob medida (personalizadas) que podem ajudar as pessoas a satisfazerem essas necessidades (71). Em cada visita do estudo PrEP Brasil esse aconselhamento de adesão e estratégias de redução de risco foi conduzido por uma equipe devidamente treinada.

Uso de Mensagens Interativas de Texto como Apoio a adesão

O rápido crescimento de tecnologias móveis e sua popularidade mundial levou ao uso de celulares para acessar problemas dentro do sistema de saúde, de modo que telefones celulares se tornaram uma ferramenta para suporte de problemas médicos e saúde pública, sendo conhecida como "mobile health" (mHealth) (72,73), oferecendo possibilidades para diagnóstico, tratamento, intervenções e treinamentos (74).

O envio de Mensagens de texto (Short Message Service - SMS) é uma abordagem simples e de baixo custo para a comunicação em saúde para um grande número de pessoas ao mesmo tempo, sendo uma ferramenta valiosas para melhoria dos resultados de saúde (75,76). Nos últimos anos, SMS têm emergido como uma importante ferramenta de comunicação na área da saúde (77). Evidências de estudos internacionais suportam o uso de mensagens de texto como uma ferramenta para melhorar a adesão a medicamentos e comparecimento a consultas médicas agendadas. Em uma revisão sistemática, Mbuagbaw et al (2015) demonstraram que práticas médicas individuais podem utilizar intervenções de mensagens de texto para melhorar a adesão a medicamentos e comparecimento a consultas clínicas, desde que as precauções corretas relativas à confidencialidade do paciente sejam incorporadas (77). No que se refere a adesão a TAR, SMS tem sido largamente testado. De acordo com a OMS, SMS poderia ser considerado como uma ferramenta de lembrança para promoção da adesão à TAR dentro do pacote de intervenção(78). Uma recente meta-análise forneceu informações adicionais evidenciando que o uso de intervenções de SMS podem melhorar a adesão a TAR quando comparado ao atendimento padrão (79).

Da mesma forma, existe um grande interesse no desenvolvimento de aplicativos para celulares no que se refere a prevenção do HIV (80). Em estudo-piloto realizado entre voluntários participando da fase aberta do ensaio clinico IPrEX, o suporte utilizando mensagens de texto mostrou-se factível e aceitável, principalmente entre os participantes mais jovens, melhorando a adesão a PrEP (81). Sullivan e colaboradores desenvolveram um aplicativo para celular baseado em teoria para fornecer um pacote de serviços para prevenção do HIV para HSH que se mostrou aceitável entre os HSH em Atlanta e Seattle (80). Atualmente, um estudo randomizado está em andamento para avaliar um aplicativo de celular para HSH e TrMT jovens não infectados pelo

HIV para melhorar a adesão a PrEP (P3: Prepared, Protected, emPowered) (82)

1.4.3. Barreiras e Facilitadores para o uso de PrEP Oral

A adesão à PrEP oral varia substancialmente entre estudos e populações. Os principais motivos relacionados a não adesão tem sido uma baixa percepção de risco para infecção pelo HIV, presença de efeitos colaterais, estigma e incompatibilidade do regime de dosagem (83). Uma revisão sistemática recente analisou postagens de mídias sociais e identificou barreiras e facilitadores para o uso de PrEP oral que não estavam presentes em artigos indexados revisados por pares. Dentre os facilitadores identificados, podemos citar "Médicos sensíveis à raça e à pobreza", "Efetividade mesmo com doses perdidas", "Possibilidade de uso de PrEP apenas para períodos de alto risco". As barreiras identificadas incluíam "Falta de acesso à saúde", "Falta de compreensão adequada da ciência por trás da PrEP pelo público e o fato de os " Outros assumirem promiscuidade " (84).

Uma pesquisa online coordenada pelo INI/FIOCRUZ, incluiu 19.457 HSH do Brasil, México e Peru e identificou os principais facilitadores e barreiras para uso da PrEP oral diária. Os facilitadores identificados foram: a PrEP sem custo, acesso ao teste gratuito de HIV, acesso a outros exames gratuitos e acesso ao aconselhamento pessoal de PrEP. As principais barreiras relatadas foram medo de não estar 100% protegido contra o HIV, medo de efeitos colaterais e medo de que a terapia antirretroviral não funcionaria caso a pessoa fosse infectada (85).

1.5.IMPLEMENTAÇÃO DA PROFILAXIA PRÉ-EXPOSIÇÃO AO HIV: UM PROJETO DEMONSTRATIVO – PREP BRASIL

A Organização Mundial de Saúde (OMS) enfaticamente recomenda que os países desenvolvam estudos de demonstração da implementação dessa estratégia de prevenção a fim de que possam ser identificados e adequadamente encaminhados os problemas para a implementação dessas estratégias em larga escala. Os dados produzidos a partir de estudos de demonstração irão subsidiar as ações para a introdução da PrEP nos programas de prevenção do HIV, tanto nos países de alta prevalência como nas epidemias concentradas como as que afetam os HSH em muitos países, tais como o Brasil.

O projeto PrEP Brasil foi um estudo prospectivo, aberto, multicêntrico, demonstrativo de PrEP, que avaliou a aceitação, segurança e viabilidade de FTC/TDF administrado por via oral, uma vez ao dia, para HSH e TrMT em risco para infecção pelo HIV. O estudo avaliou os componentes-chave da implementação da PrEP em 3 centros de pesquisa nas cidades do Rio de

Janeiro e São Paulo: o Instituto Nacional de Infectologia Evandro Chagas-Fiocruz, o Centro de Referência e Treinamento em DST e AIDS de São Paulo e a Universidade de São Paulo (41,86).

Os desdobramentos do estudo PrEP-Brasil são de extrema importância científica e social. Em 2017, a Comissão Nacional de Incorporação de Tecnologias no SUS (CONITEC) recomendou a incorporação da associação de FTC/TDF como PrEP para populações sob risco aumentado de infecção pelo HIV no SUS (87).

A importância do estudo PrEP-Brasil não se resume somente às enormes contribuições que a demonstração do uso de PrEP na nossa população irão trazer, mas também foi um marco para uma série de ações específicas para atender às necessidades dessa população altamente vulnerável, das quais podemos citar, estudos para população de mulheres transexuais ("PrEParadas" e "Modelo de atenção para mulheres transexuais e travestis: transcendendo barreiras"), além das comemorações do dia da visibilidade trans onde a cada ano são promovidos encontros com a sociedade para promover um amplo debate em torno dos direitos e cidadania de mulheres e homens trans.

2. JUSTIFICATIVA

Apesar de décadas de esforços e avanços na prevenção, a infecção pelo HIV ainda é uma pandemia global com 36,9 milhões de pessoas vivendo com HIV em 2016 (1). Nos últimos anos houve um grande avanço no conhecimento sobre PrEP, principalmente com a demonstração de que seu uso reduz significativamente o risco da aquisição de HIV (20–25). No que se refere à eficácia, os estudos iPrEX e CAPRISA demonstraram uma dose-resposta clara com níveis de proteção diretamente proporcional à adesão ao produto (19,20), evidenciando que a adesão é crítica e fundamental para maximizar a eficácia da PrEP na prevenção do HIV (48,49). Neste sentido, houve um aumento da atenção sobre os potenciais grupos-alvo para uso de PrEP oral e sobre como a otimização da adesão pode maximizar a prevenção (88). Se por um lado existe uma vasta literatura referente ao apoio e adesão a TAR no contexto terapêutico, por outro, pouco se conhece sobre os meios de apoiar a adesão no contexto profilático entre indivíduos saudáveis, não infectados pelo HIV (88). Embora os projetos de demonstração de PrEP estejam oferecendo intervenções para promover a adesão à PrEP, como por exemplo, fornecimento de folhetos educativos, uso de telefones e SMS e aconselhamento de redução do risco, eles não objetivam avaliar a eficácia das abordagens adotadas. Neste sentido, a avaliação da concordância entre a exposição ao medicamento e outras medidas de adesão indireta em um programa de PrEP de saúde pública do mundo real é de grande importância no cenário clínico, uma vez que essas medidas podem ser úteis no monitoramento do uso de PrEP no contexto do SUS. Adicionalmente, a compreensão dos fatores associados à adesão à PrEP (barreiras e facilitadores), bem como a utilidade do uso de tecnologias (ex. SMS), pode ajudar no desenvolvimento de estratégias para apoiar, motivar e sustentar o uso da PrEP, sendo de grande importância para maximizar o impacto do uso da PrEP na saúde pública, principalmente nas populações de alto risco.

3. OBJETIVOS

3.1. OBJETIVO GERAL

Estudar e avaliar a adesão à PrEP entre HSH e TrMT incluídos em um estudo demonstrativo.

3.2.OBJETIVOS ESPECÍFICOS

- Examinar a concordância entre três medidas de adesão indireta (taxa de posse de medicamento, contagem de comprimidos e autorrelato) e níveis de medicamento altamente protetores;
- Avaliar o impacto do uso de SMS na adesão à PrEP;
- Avaliar os preditores de adesão autorrelatada à PrEP;
- Avaliar as barreiras e facilitadores percebidos para adesão a PrEP.

4. ESTRUTURA DA TESE

Os capítulos de metodologia, resultados e discussão foram apresentados na forma de três artigos:

1. **Performance of HIV pre-exposure prophylaxis indirect adherence measures among men who have sex with men and transgender women: Results from the PrEP Brasil Study** (Performance de medidas de adesão a profilaxia pré-exposição indiretas entre homens que fazem sexo com homens e mulheres transexuais: resultados do estudo PrEP Brasil)

2. **Randomized controlled trial of daily text messages to support adherence to daily oral pre-exposure prophylaxis (PrEP) among men who have sex with men (MSM) and transgender women (TGW): PrEP Brasil SMS Pilot Substudy** (Estudo randomizado de mensagens de texto diárias para apoio a adesão a profilaxia pré-exposição entre homens que fazem sexo com homens (HSH) e mulheres transexuais (TrMT): Subestudo Piloto de SMS do PrEP Brasil)

3. **Predictors of self-reported adherence to pre-exposure prophylaxis (PrEP), including barriers and facilitators, among men who have sex with men (MSM) and transgender women (TGW): PrEP Brasil Demonstration Study** (Preditores de adesão autorrelatada a profilaxia prè-exposição, incluindo barreiras e facilitadores entre entre homens que fazem sexo com homens (HSH) e mulheres transexuais (TrMT): Estudo Demonstrativo PrEP Brasil)

5. PRIMEIRO ARTIGO

Autores:

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PLOS ONE

RESEARCH ARTICLE

Performance of HIV pre-exposure prophylaxis indirect adherence measures among men who have sex with men and transgender women: Results from the PrEP Brasil Study

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Abstract

Introduction

Efficacy of daily emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for PrEP is strongly dependent on the adherence. We examined the concordance between indirect adherence measures and protective drug levels among participants retained through 48 weeks in the PrEP Brasil Study.

Methods

PrEP Brasil was a prospective, multicenter, open-label demonstration project evaluating PrEP provision for men who have sex with men (MSM) and transgender women (TGW) at higher risk for HIV infection within the setting of Brazilian Public Health System. Three indirect adherence measures were obtained at week 48: medication possession ratio (MPR), pill count and self-report (30-days recall). Tenofovir diphosphate (TFV-DP) concentration in Dried Blood Spot (DBS) was measured at week 48. Areas under (AUC) the receiver operating characteristics (ROC) curve were used to evaluate the concordance between achieving protective drug levels (TFV-DP$\geq$700fmol/punch) and the indirect adherence measures. Youden's index and distance to corner were used to determine the optimal cutoff points for each indirect adherence measure. We calculated sensitivity, specificity, negative (NPV) and positive (PPV) predictive values for the found cutoff points. Finally, Delong test was used to compare AUCs.

Results and discussion

From April, 2014 to July, 2016, 450 participants initiated PrEP, 375(83.3%) were retained through 48 weeks. Of these, 74% (277/375) had TFV-DP $\geq$700fmol/punch. All adherence

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Competing interests: The authors have declared that no competing interests exist.

measures discriminated between participants with and without protective drug levels (AUC>0.5). High indirect adherence measure was predictive of protective drug levels (PPV>0.8) while low indirect adherence measure was not predictive of lack of protective drug levels (NPV<0.5). No significant differences were found between the adherence methods (p = 0.44).

Conclusions

Low-burden measurements such as MPR and self-report can be used to predict PrEP adherence in a public health context in Brazil for MSM and TGW retained through 48 weeks.

Clinical Trial Number: NCT01989611.

Introduction

Pre-exposure prophylaxis (PrEP) refers to the use of antiretroviral medications (ARV) by HIV-negative individuals aiming to reduce their risk of HIV infection. It is one of the most promising strategies in the field of biomedical HIV prevention [1]. The efficacy and safety of oral tenofovir disoproxil fumarate plus emtricitabine (FTC/TDF) as PrEP has been demonstrated in several trials [2–7]].

Cumulative evidence provided by iPrEX study[2], Partners PrEP [8] and TDF2 trial [6] led the United States Food and Drug Administration (FDA) to approve daily FTC/TDF for PrEP in July 2012 [9]. Now PrEP is available in numerous countries, including Brazil, where since December 2017, it has been offered as a public health policy to populations at high risk of acquiring HIV, as men who have sex with men (MSM) and transgender women (TGW) [10].

Brazil has been a pioneer in Latin America HIV/AIDS policies for both treatment and prevention [11], with universal free access to ARV and human rights-based prevention programs centered on behavioral and structural interventions [12]. Following the accumulated evidence on PrEP efficacy, since 2013 the Brazilian Ministry of Health (MoH) has supported projects on acceptability and feasibility of PrEP use in the country so as to generate evidence for the construction of the PrEP national policy [13]: PrEP Brasil [14]; Combina Project; PrEParadas Study; Horizon Project; Transgender Women Project Federal University of Bahia and ImPrEP [15]. PrEP demand was estimated to be 66,000–98,000 of Brazilian MSM aged 15–64 years [16] and from January to September 2018, 5,712 individuals initiated PrEP provided by the MoH [17].

Adherence is a critical component to PrEP effectiveness and high levels of PrEP use are essential to maximize the public health impact of this prevention strategy [18,19]. During PrEP Brasil study, the main barriers to PrEP adherence were forgetting doses, change in daily routine, pills shortage and not having pills available at the time of dose. The three main facilitators were associating PrEP with some daily activity, being engaged with PrEP and keeping the tablets in some visible place [20]. More recently, an online survey conducted among 11,367 Brazilian MSM found the main barriers to PrEP use to be related to information about PrEP such as fear of not being 100% protected against HIV, of side effects, and that ART would not work if infected. PrEP with no cost, access to free HIV test and access to personal PrEP counseling were the main facilitators of PrEP use [21].

A pharmacokinetic modeling study demonstrated the relationship between PrEP use and protective efficacy, showing that adherence is essential for maximizing the effectiveness of PrEP [3,22,23]]. However, accurate assessment of adherence is challenging. Existing methods

of assessing adherence are limited for various reasons that have been well described in the literature [23–27]], and there is no gold standard for adherence measurement [24,28]. Drug concentration levels could be considered the most accurate measure to quantify adherence, but the high costs of available methodologies make it unfeasible for implementation in routine clinical practice, especially in a public health context [28].

In this study, we examined the concordance between three indirect adherence measures (medication possession ratio, pill count and self-report) and highly protective drug levels measured from dried blood spot (DBS) among participants retained through 48 weeks in the PrEP Brasil Study.

Methods

As described in detail previously [14,29], PrEP Brasil was a prospective, multicenter, open-label demonstration project evaluating PrEP provision for MSM and TGW at higher risk for HIV infection in the context of the Brazilian Public Health System. Study design and 48-weeks' results on retention, engagement, ethics and adherence measured by drug levels were published elsewhere [14]. All procedures were conducted according to the principles expressed in the Declaration of Helsinki. The present analysis was approved by INI-Fiocruz Review Board (#08405912.9.1001.5262).

Participants received a bottle containing 30 pills of FTC/TDF at enrollment and, subsequently, were provided with a sufficient supply of pills for daily treatment until the next study visit (weeks 4, 12, 24, 36 and 48). Study pharmacists instructed the participants to take one tablet daily and advised them to return FTC/TDF pills in the original bottle to the pharmacy, whether used or not. At each study visit, the pharmacists provided adherence support and counseling. At week 48, we measured adherence using three different methods: (a) medication possession ratio (MPR); (b) pill count; and (c) self-report.

MPR reflects the days the participant is "covered" by the study medication. It is calculated by the ratio of the number of pills dispensed at the prior visit and the number of days between that visit and the week 48 visit. MPR values equal or greater than 1.00 indicate 100% coverage, and values below 1.00 reflect that the participant was not covered by the study medication during all the days between week 48 and the prior visit [30].

Pill count was calculated by the number of pills dispensed at the prior visit minus the number of pills returned at week 48, divided by the number of days between the two visits. Values are given in percentage. We could not calculate pill count for the participants who did not return any bottle of study medication for counting at week 48. These cases were considered missing data and not included in the accuracy analysis (n = 42).

Self-report was assessed using one question from a structured questionnaire ("**On average for how many days did you forget to take FTC/TDF in the previous 30 days?**") administered by study pharmacists. Values are given in percentage. Participants attending the week 48 visit who refused to answer the questionnaire (n = 28) were considered missing and not included in the accuracy analysis.

DBS specimens were collected for tenofovir diphosphate (TFV-DP) assessments for all participants who attended the week 48 visit. TFV-DP levels were measured using liquid chromatography-mass spectrometry tandem mass spectrometry (LC-MS/MS) at the University of Colorado Antiviral Pharmacology Laboratory (Aurora, CO, USA) with standard procedures [3,31,32]].

Results from iPrEX Open-label study demonstrated the following correspondence of doses taken per week, TFV-DP concentration and levels of protection: a TFV-DP concentration $\geq$700 fmol/punch, corresponding to $\geq$4 doses/week, was associated with a 100% (95% CI 86%

to 100%) reduction in HIV transmission risk; and a TFV-DP concentration of 350–699 fmol/punch, corresponding to 2–3 doses/week, was associated with a 86% (21% to 99%) reduction in HIV transmission risk [3]. For the purposes of this analysis, TFV-DP levels were dichotomized as highly protective drug levels (≥ 700 fmol/punch) vs. poorly protective drug levels (<700 fmol/punch) [33].

The area under the curve (AUC) was estimated using a receiver operating characteristics (ROC) curve analysis to evaluate the accuracy of each indirect adherence measure in discriminating between those with or without highly protective drug levels. From the ROC curve, the optimal cutoff points for discriminating between those with or without protective drug levels were found based on the Youden index and the distance to corner [34–36]. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for the cutoff points were calculated. Statistical comparisons of the AUC for each adherence measure were performed with the DeLong test, a nonparametric method commonly used to identify differences among AUC [37]. This method does not assume the strong normality assumptions that the alternative Binormal method makes. Analyses were conducted using SAS version 9.4 (SAS Institute, North Carolina, USA).

Results

From April 2014 to July 2016, 450 participants initiated PrEP, of whom 375 (83%) were retained for 48 weeks. Table 1 depicts baseline characteristics for the 375 participants included compared with the 75 participants not included in this analysis. The full baseline characteristic for these participants are presented in previous work by the authors [14]]. At week 48, 277 (74%) of the 375 participants had highly protective drug levels consistent with at least four

Table 1. Baseline characteristics of participants included in this analysis vs. not included.

	Total	Included n (%)	Not included n (%)	p-value
Overall	450	375 (83)	75 (17)	
Site Location				
RJ	180	150 (83)	30 (17)	1.00
SP	270	225 (83)	45 (17)	
Age				
18–24 years	113	92 (81)	21 (19)	0.52
25–34 years	214	179 (84)	35 (16)	0.83
≥35 years	123	104 (85)	19 (15)	
Schooling				
< 12 years	115	93(81)	22(19)	0.41
≥ 12 years	335	282(84)	53(16)	
Color/Race				
White	243	205(84)	38(16)	
Black	57	47(82)	10 (18)	0.72
Mixed	145	118 (81)	27 (19)	0.45
Gender				
Male	425	354 (83%)	71 (17%)	0.93
Transwomen	25	21 (84%)	4 (16%)	
Steady partner				
Yes	233	194 (83%)	39 (17%)	0.87
No	204	171 (84%)	33 (16%)	

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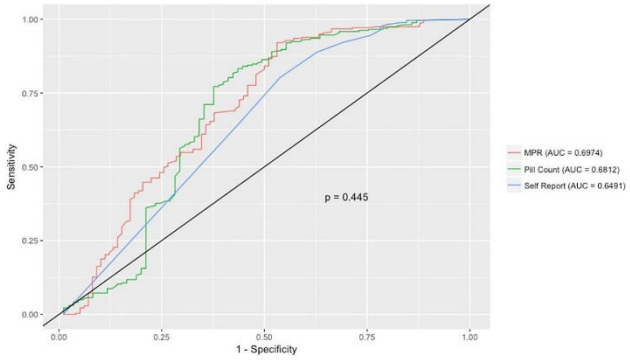

Fig 1. ROC curves for protective drug level vs indirect adherence measures. ROC curves of indirect adherence measures to predict protective drug levels. (*) P-value refers to the difference between the AUC of the three indirect adherence measures (De Long's test).

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doses per week [14]]. Median adherence rates were 1.10 (IQR 0.98–1.31) for MPR, 97.14% (IQR 88.89–100.00) for pill count and 100.00% (IQR 93.33–100.00) for self-report. Among 42 participants who did not return any bottle of FTC/TDF for pill count, 35.7% and 64.3% had high and low protective drug levels, respectively. As for the 28 participants who did not complete the self-report questionnaire, 28.6% and 71.4% had high and low protective drug levels, respectively.

According to the ROC curves, the three indirect adherence measures can predict highly protective drug levels at week 48 (Fig 1). The area under the ROC curve was 0.70 for MPR, 0.68 for pill count and 0.65 for self-report.

The cutoff value associated with highly protective levels of TFV-DP according to the highest Youden index was 1.07 for MPR, 90.09% for pill count and 99.90% for self-report (Table 2). The proportion of participants with adherence values equal to or higher than the cutoff point was as follows: 62.9% for MPR (236/375); 72.4% for pill count (241/333); and 59.6% for self-report (207/347).

The concordance between the adherence methods, in terms of positive predictive values (PPV) and negative predictive values (NPV), is depicted in Table 2. For all indirect adherence measures, high indirect adherence measures were predictive of protective drug levels (PPV>0.8), while low recorded adherence was not predictive of a lack of protective drug levels (NPV<0.5).

Comparison using the DeLong test showed no significant differences between the three indirect adherence measures in the ability to discriminate participants with and without protective drug levels (p = 0.44).

Table 2. Association between indirect adherence measures and protective drug levels.

Adherence measures	AUC (95% CI)	P-value	Cutoff point	Sensitivity	Specificity	PPV	NPV
MPR	0.70(0.63–0.76)	<0.001	1.07	0.68	0.62	0.84	0.41
Pill count	0.68(0.60–0.76)	<0.001	90.09	0.77	0.62	0.86	0.47
Self-report	0.65(0.58–0.72)	<0.001	99.90	0.64	0.56	0.84	0.31

MPR = medication possession ratio; PPV = positive predictive value; NPV = negative predictive value.

https://doi.org/10.1371/journal.pone.0221281.t002

Discussion

The main purpose of this study was to assess the concordance between a pharmacologic measure of exposure and "traditional", feasible and low-cost adherence measures (pill count, medication possession ratio and self-report). This is the first study to evaluate the correlation of indirect adherence measurements in the context of a public health program in a middle-income country. As previously mentioned, PrEP efficacy is strongly dependent on adherence, thus, the identification of whether an individual in a PrEP Program is adherent or not is of great importance in the clinical setting. Each adherence measure has its strengths and weaknesses [26,27].

We observed high levels of adherence among participants retained through 48 weeks in PrEP Brasil study using all indirect adherence measurements (MPR, pill count and self-report) as well as by TFV-DP levels [14]. High adherence levels based on drug levels diverge from previous placebo-controlled PrEP trials [2,28,38,39], but such levels are consistent with findings from recent open-label and demonstration projects [28,40–43]. This result was expected, as people feel more comfortable using PrEP once more safety and efficacy results become available, and when such results are obtained outside a placebo-controlled study [28,44]. We observed low levels of adherence based on drug levels for those who did not return their bottles for pill count and for those who chose not to answer the self-report measure. Although a great effort was made to perform these assessments in a neutral supportive environment without judgment or direct persuasion, we suppose, given their low levels of adherence, that these individuals wanted to avoid any discomfort or fear to report socially undesired behavior.

Our results showed that all indirect adherence measures could discriminate participants with and without protective drug levels with fair discriminatory ability (AUC>0.5) among participants retained through 48 weeks. Additionally, there were no differences between the three indirect adherence measures in the ability to discriminate between participants with and without protective drug levels. The efficacy of adherence measures in discriminating between achieving or not achieving protective drug levels vary among clinical trials, a finding that can be explained by the differences in the study location and demographic characteristics. The results from iPrEx placebo-controlled trial which included 510 participants in 6 countries (Brazil, Ecuador, Peru, South Africa, Thailand and US) showed that only MPR was able to discriminate, with relatively poor discriminatory ability [30]. The Partners PrEP ancillary adherence study among East African serodiscordant couples also found poor discriminatory ability for self-report (AUC 0.56 [95% CI, 0.47–0.61]) and pill count (AUC 0.58 [95% CI, 0.46–0.60]) [42]. Likewise, the ATN-123 found that self-report could not accurately capture true levels of medication adherence among young MSM in US [45]. Nonetheless, the TDF2 PrEP trial in Botswana found a modest correlation between TFV drug levels and self-reported adherence (phi-coefficient = 0.28), and a weaker relationship between drug levels and pill count adherence (phi-coefficient = 0.20) [46]. The iPrEx open-label extension also found concordance for self-report with PPV and NPV of 83% (95% CI, 81.3–84.3) and 82% (95% CI, 81.3–84.3), respectively [47]]. We also determined the best cutoff points to discriminate high levels of adherence. Considering these cutoff values, PPV values for the three indirect adherence measurements were higher than 0.80. This means that approximately 80% of individuals with adherence higher than the cutoff values also have high adherence based on TFV-DP levels; thus, high recorded adherence was predictive of highly protective levels. Although all indirect adherence measures presented high PPV, it is important to emphasize that the possibility of "false positive" responses must be considered within clinical practice, once individuals presenting high indirect adherence measure may not achieve highly effective level of protection and thus be at risk of HIV. This could prevent the access of these individuals to adherence support (adherence counseling, for example). The use of 2 or more adherence measures may be useful

to identify more efficiently low adherence in "real world", as discussed in the "WHO consultation on PrEP adherence" [48]. Abaasa et al.[49] demonstrated the incremental value of combining adherence measures (electronic monitoring, self-report, and drug concentrations in plasma and hair). However, the authors used objective adherence measures, so more studies are needed on how the use of two or more indirect adherence measure can give an accurate picture of PrEP adherence.

Conversely, NPV values were low (<0.5), indicating that low recorded adherence was not predictive of a lack of protective drug levels. This finding can be explained by the fact that a highly protective drug level (≥700fmol/punch) can be achieved with less frequent dosing (4 pills/week) than the current approved recommendation of daily PrEP. Even those with low measured adherence may still have protective drug levels. It means that for achieving highly effective levels of protection (TFV-DP≥700fmol/punch) the average adherence over the period must be approximately 57% (4 taken doses/7 days = 0.57). It is important to note that the best cutoff points estimated in our study (1.07; 90.09% and 99.90%, for MPR, pill count and self-report, respectively) are higher than 57%, thus it is plausible that an individual with adherence lower than a given cutoff point could still achieve levels of protection.

Self-report is the most common adherence measure in clinical practice [50]. The major strengths of this measure are ease of collection, low cost and the accuracy of reported non-adherence [26]. Conversely, it depends on the participants' memory or comfort in providing truthful information [51], thus this measurement is subject to bias (recall and social desirability bias) which often lead to overestimation of adherence. A way to improve self-report adherence is providing an environment where the individual feels at ease and confident in reporting socially undesired behavior [26]. Pill count is a more objective adherence measure and more accurate when compared to self-report. This measure is also easy to collect and relatively inexpensive [26], though, as limitations, it is time consuming and subject to manipulation (for example, pills discarded, lost or shared with others) and might not reflect the pattern of PrEP use [27,52]. MPR is derived through dispensation records, it corresponds to the percentage of days during which individuals are in possession of their medications [53] reflecting the pill coverage during a given time. Similarly to pill count, MPR do not provide PrEP pattern use as it indicates pharmacy dispensation rather than drug ingestion. MPR above 1.0, for example, does not necessary mean over adherence, but indicates that an individual possesses enough medication to cover a given time of PrEP use. According to "WHO consultation on PrEP adherence", pharmacy refill "may be interpreted as maximal predicted PrEP adherence" [48]. MPR may be a powerful tool for adherence assessment, especially if dispensation information is accurate and accessible. The Brazilian experience with SICLOM (the National Computerized System for the Control of Drug Logistics)—which contains specific information about antiretroviral dispensation, including PrEP—suggests that this type of database could provide a unique data source for adherence assessment in the country and perhaps elsewhere [54]].

The present study has some limitations. First, the different time periods associated with each indirect adherence measure assessment (30-day recall for self-report, 90-day recall for pill count and MPR) and TFV-DP assessment (a 17-day half-life corresponding to cumulative adherence over 1–3 months) may impact comparisons. It is a common limitation when comparing a pharmacokinetic measure with a non-pharmacokinetic measure [30,42,49]. TFV-DF levels in DBS has a long half-life of 17 days, which provides an average adherence of 1 to 3 months[31,48], as red blood cells live in blood circulation for 100 to 120 days [55]. However, neither TFV-DF levels nor indirect adherence measures (MPR, pill counts and self-report) can provide patterns of FTC/TDF scheduling use over the mentioned period. Despite the different periods of assessment, the rationale for this analysis was to seek evidence on whether the three indirect adherence measures could or not discriminate participants that achieved highly-

effective level of protection by using at least an average of 4 doses/week of PrEP, independently of the FTC/TDF scheduling use. Furthermore, it is already well established that through the determination of drug levels of TFV-DF in DBS we are able to assess the adherence "categories" of a given individual (7 doses/week; ≥ 4–7 doses/week; 2–3 doses/ week and <2doses/ week). These categories have been used in PrEP demonstration projects to estimate gradients of adherence [56]. Second, TFV-DP levels were dichotomized as highly protective drug levels or poorly protective drug levels, limiting the interpretation of correlation data from this analysis. Third, drug levels were assessed for participants attending the week 48 visit, thus we assessed the performance of indirect adherence measures only for these participants. Though this limitation could have led to selection bias, we argue that, if any, the impact was minimal. We have previously reported that there was no significant difference on baseline characteristics between participants retained and not retained at week 48. Importantly, there was no difference in the levels of TFV-DP measured at week 4[29]. Fourth, the concordance between the indirect adherence measures was only obtained for the best cutoff points according to the aim of this study. For our analysis, we chose to give equal weight to sensitivity and specificity. Youden's index and distance to corner were then used, and each sensitivity and specificity combination in the output was considered. Lastly, the low levels of adherence based on drug levels for those considered missing for pill count and self-report may have led to an overestimation in the discriminatory ability of these indirect adherence measures.

Conclusions

In conclusion, this study provided the opportunity to assess the concordance between drug exposure and other indirect adherence measures in a real-world public health PrEP program. Our results highlight the utility of low-burden measurements such as MPR and self-report in predicting adherence among our target population. These measurements can be useful in monitoring PrEP use among MSM and TGW retained in a PrEP program and in guiding the need for adherence interventions. Studies on incremental value of combining MPR and self-report in predicting adherence among our target population are needed.

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6. SEGUNDO ARTIGO

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Randomized controlled trial of daily text messages to support adherence to daily oral pre-exposure prophylaxis (PrEP) among men who have sex with men (MSM) and transgender women (TGW): PrEP Brasil SMS Pilot Substudy

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Randomized controlled trial of daily text messages to support adherence to daily oral pre-exposure prophylaxis (PrEP) among men who have sex with men (MSM) and transgender women (TGW): PrEP Brasil SMS Pilot Substudy

Abstract

Background. Short message service (SMS) has emerged as an important communication tool in the health arena. We evaluated the effectiveness of SMS in improving adherence to daily emtricitabine/tenofovir for PrEP among men who have sex with men (MSM) and transgender women.

Methods. All participants of PrEP Brasil study were invited for the PrEP Brasil SMS Pilot Substudy at the screening visit and those who agreed were randomized 1:1 to standard-of-care (SoC) or intervention (SMS) arms. SMS messages were launched weekly to participants for 48 weeks. We defined adequate adherence to PrEP as having medication possession ratio (MPR) ≥1.02, which was the best cutoff point for achieving protective drug level of tenofovir-diphosphate concentrations (≥700fmol/punch) at weeks 4 and 48. We used generalized estimating equation models to access the predictors of adherence and non-adherence to PrEP.

Findings. From 450 participants included on PrEP Brasil, 417(92.7%) were randomized to the substudy: 210 to SoC and 207 to SMS. A total of 347(83.2%) participants completed the study, and there was no difference between arms on retention at week 48. A greater proportion of participants in the SMS arm had adequate adherence to PrEP throughout the study. In multivariable model, SMS intervention was a predictor of adequate PrEP adherence (AOR 1.37; CI 95%:1.07-1.75) when adjusted by study visit, site location, age, condomless receptive anal sex and binge drinking. Being from São Paulo (AOR= 1.42; CI 95%:1.10-1.85) and having condomless receptive anal sex (AOR=1.40; CI 95%:1.09-1.80) increased the odds of adequate PrEP adherence while being 18-24 years (AOR= 0.69; CI 95%:0.48-0.99) and reporting binge drinking (AOR=0.72; CI 95%:0.55-0.92) decreased the odds of adequate PrEP adherence.

Interpretation. SMS-intervention improved adequate PrEP adherence and can be a useful tool to prevent PrEP shortage. Future interventions and web-based strategies to increase PrEP adherence among the youngest should be evaluated.

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Research in context

Evidence before this study

Over the past few years, studies have demonstrated that the use of oral emtricitabine/tenofovir as preexposure prophylaxis (PrEP) by HIV-infected individuals can substantially decrease HIV transmission. Levels of protection are directly proportional to adherence. In this sense, adequate levels of adherence are critical and essential to maximize the public health impact of this biomedical prevention technology. We have previously demonstrated that medication possession rate (MPR) can be a powerful tool for adherence assessment, especially if drug dispensation information is accurate and easily accessible, as in Brazil. Short message service (SMS) is a useful strategy to improve health outcomes including antiretroviral adherence in the context of HIV treatment. SMS messages may increase adherence to oral PrEP.

Added value of this study

PrEP Brasil demonstration study explored the acceptability, safety and use of PrEP among men who have sex with men (MSM) and transgender women in three Brazilian sites. Results from PrEP Brasil were essential for the implementation of PrEP within the country's public health system. The PrEP Brasil SMS Pilot Substudy was the first randomized study to evaluate the effect of this mHealth intervention to improve adherence to oral PrEP in the context of a public health program in America Latina. A total of 417 individuals were randomized (1:1) to receive SMS messages or only standard of care for 48 weeks. SMS messages improved adequate adherence to daily oral PrEP during the study.

Implications of all the available evidence

Automated text messaging interventions is a low-cost intervention that could be implemented to increase PrEP adherence among MSM and transgender women.

Introduction

The Safety and efficacy of oral emtricitabine plus tenofovir disoproxil fumarate (FTC/TDF) in reducing the risk of HIV infection when used as Pre-exposure prophylaxis (PrEP) has been demonstrated in clinical trials (1–6). The relationship between PrEP uptake and protective efficacy has been also well-demonstrated (7–9). Although adherence has been a requisite to PrEP protection (10), there are few empirical studies supporting adherence interventions on that field (11).

Despite the global advances in the treatment and prevention of HIV infection, the HIV epidemic disproportionately affects certain key population like and transgender women (TGW), men who have sex with men (MSM), people who inject drugs, sex workers and prisoners (12,13). According to UNAIDS, 47% of the new HIV infections globally in 2017 were among key populations and their sexual partners (12). Studies show that MSM and TGW are respectively 19 times and 50 times more likely to have HIV than the general adult population (13). Despite the clear need for intervention, resources for HIV prevention and treatment programs for these populations remain scarce (12).

The rapid grown of mobile technologies and their popularity worldwide led to solutions to address problems within health care systems. Thus, mobile phones have become popular tools to support medical or public health (mHealth) (14,15), offering new possibilities for diagnosis, treatment, interventions, applications, and training (16). Text messaging, including Short Message Service (SMS), is a simple, low-cost approach for health communication to a large number of people and offers valuable tools in improving healthcare outcomes (17,18). Text messaging to support antiretroviral therapy (ART) adherence has been widely used and tested. According to the World Health Organization (WHO) consolidated ART guidelines SMS could be considered as a reminder tool for promoting adherence to ART as part of a package of adherence interventions (19). Results from two meta-analysis have shown that mobile phone text messaging are efficacious in enhancing adherence to ART compared to standard care (SoC) and support the use of SMS in a weekly basis (15,20).

In this sense, there is a wide interest in the scientific development and use of mobile phone applications (apps) on the field of HIV prevention (21). Fuchs and colleges demonstrated that a weekly bidirectional SMS was feasible, highly acceptable and efficacious to improve PrEP adherence (22). Sullivan and colleges verified that a theory-based mobile phone app to provide information on HIV prevention technologies and services was acceptable among Android-using MSM from Atlanta and Seattle, USA (21). A randomized controlled trial is ongoing to evaluate

an app using social networking and game-based mechanics to improve PrEP adherence among young MSM and young TGW (P3 - Prepared, Protected, emPowered) (23).

This study aimed to evaluate the effectiveness of SMS in improving adherence to daily oral FTC/TDF for PrEP among MSM and TGW.

Methods

Study Design and Population

PrEP Brasil was a prospective, multicenter, 48-week open-label demonstration study assessing PrEP delivery for MSM and TGW at higher risk for HIV infection in the context of the Brazilian Public Health System (SUS). Details of PrEP Brasil study design and 48-weeks results on retention, engagement, and adherence were published elsewhere (24).

PrEP Brasil SMS Pilot Substudy was a randomized controlled trial to evaluate the effectiveness of weekly SMS in improving adherence to daily oral FTC/TDF for PrEP among participants of the PrEP Brasil Study.

Eligibility, Recruitment and Informed Consent

PrEP Brasil SMS Pilot Substudy was offered to all participants of PrEP Brasil study. Individuals were eligible if they had an SMS-capable mobile phone and were willing to use this phone for receiving study text messages. PrEP provision, clinical assessments, safety monitoring and tenofovir-diphosphate (TFV-DP) level were obtained per the parent protocol.

PrEP Brasil SMS Pilot Substudy was approved by the Institutional review boards at Instituto Nacional de Infectologia Evandro Chagas (INI-Fiocruz; Rio de Janeiro, Brazil), Universidade de São Paulo (USP; São Paulo, Brazil), and Centro de Referência e Treinamento DST/AIDS de São Paulo. All participants provided consent to participate in the substudy. The study was conducted according to the principles expressed in the Declaration of Helsinki.

Randomization and Mask

Eligible participants were randomized 1:1 to two intervention arms: Standard of Care (SoC) or SoC plus SMS (SMS). The random numbers were generated by an Internet web-based interface. A research staff not involved in subject care was responsible for randomization procedures. The study clinical staff was not blinded to the intervention arm assigned.

Standard of Care (SoC) Procedures

The study sites were instructed to maintain the local standard of care procedures regarding PrEP adherence, which included psychologist and pharmacist counseling to mitigate adherence barriers.

Development of an automated password-protected messaging system platform

INI-Fiocruz Information Technology staff developed an automated password-protected messaging system platform. This platform had technical safeguards to protect participant information and confidentiality as only authorized study staff (including the study coordinator) using a personal username and password had access to the platform. The study coordinator was responsible to include the participants' mobile numbers allocated to SMS arm into the platform. Through the password-protected platform database the authorized staff could supervise the SMS messages exchanged with the participants. The platform access and integrity could only be monitored and audited under an authorized staff supervision. Additionally, the platform had protection against unauthorized access.

SMS messages

All participants allocated to SMS arm received a morning weekly SMS message ("Are you okay?" in the local language) from the automated platform. Participants were instructed to respond "YES" or "no". Those who answered "YES" received an acknowledgement "THANK YOU" text message. The study coordinator contacted all participants replying "NO" within 48 hours and provided adherence support. For the participants not responding the initial SMS message, the platform automatically sent a second SMS at night. The study coordinator contacted by phone all participants not responding for three consecutive weeks (Figure 1). We instructed the participants to not use the SMS messages for medical emergency. Instead, they were instructed to contact the study site by phone number or to proceed immediately to the site.

Adequate PrEP adherence

We used medication possession ratio (MPR) to evaluate PrEP adherence at weeks 4, 12, 24, 36 and 48. MPR reflects the days the participant is "covered" by the study medication and it is calculated by the ratio of the number of pills dispensed at the prior visit and the number of days

between visits.

Dried Blood Spot (DBS) specimens were collected for tenofovir diphosphate (TFV-DP) assessments at weeks 4 and 48. TFV-DP levels were measured using liquid chromatography-mass spectrometry tandem mass spectrometry (LC-MS/MS) at the University of Colorado Antiviral Pharmacology Laboratory (Aurora, CO, USA) with standard procedures (2,25,26).

Results from iPrEX Open-label study demonstrated that a TFV-DP concentration ≥700 fmol/punch, corresponding to ≥4 doses/week, was associated with a 100% (95% CI 86% to 100%) reduction in HIV transmission risk (9). Previous exploratory analysis from our group suggested that MPR could discriminate individuals with and without protective drug levels at week 48 (AUC 0.70; [95% CI 0.63-0.76]) (27). For this analysis, we applied the same rational including DBS data from both weeks 4 and 48 to determine the MPR cutoff point for achieving protective drug levels (TFV-DP concentration ≥700 fmol/punch).

We defined adequate PrEP adherence as MPR values equal or superior to the calculated cutoff point.

Statistical Analysis

We conducted initial descriptive analyses to compare baseline characteristics, the randomization of participants, and distribution of variables. We used chi-square or Fisher's exact test, when appropriate, to compare the study arms.

The area under the curve (AUC) was estimated using a receiver operating characteristics (ROC) curve analysis to evaluate the accuracy of MPR in discriminating between those with or without highly protective drug levels. From the ROC curve, the cutoff point for discriminating between those with or without protective drug levels was found based on the Euclidean Distance.

We used generalized estimating equation logistic model (GEE) to evaluate time-dependent correlates of adequate PrEP adherence at each follow-up visit (weeks 4, 12, 24, 36 and 48). The factors associated with adequate PrEP adherence ($p < .10$) after adjustment for site and visit were retained in the final model. All tests were two-tailed and P-values of less than 0.05 were considered statistically significant.

Analyses were conducted using SAS version 9.4 (SAS Institute, North Carolina, USA).

Results

PrEP Brasil SMS Pilot Substudy

From April 2014 to July 2016, 450 participants were included in PrEP Brasil study, 6.9%(31/450) refused to participate in the PrEP Brasil SMS Pilot Substudy and 0.4%(2/450) were ineligible (no personal mobile phone to receive SMS messages). Of 417(92.7%) eligible participants, 207 were randomized to SMS and 210 to SoC (Figure 1). Baseline characteristics for the 417 enrolled participants according to the intervention arm are shown on Table 1. Overall, median age was 30 years (IQR: 25-35) (24.5% of participants aged 18-24 years), 59% were from São Paulo, 73.6% had ≥ 12 years of schooling, 54.4% were white and only 6.0% were TGW. A total of 347 (83.2%) participants completed the study, and there was no difference between arms on retention at week 48 (p=0.21; Figure 2).

Until study competition, 20,857 SMS were sent to the study participants. Of these, participants replied to 9,854 (47.2%) SMS messages and 11,003 (52.8%) were ignored by the participant. The vast majority of participants replied “YES” (97.1%; 9,571/9,854) and only 2.4% (237/9,860) replied “NO”. Some individuals (0.5%; 46/9,854) provided a nonstandard answer that could not be classified as "YES" or "NO”.

For the 237 “NO” messages, 26.6% (63/237) required no contact as the participant came to the clinic for an unscheduled or scheduled visit. The study coordinator tried to contact by phone all the 174 remaining messages: 53 (30.6%) participants did not answer the phone; 32 (18.5%) were facing personal problems; 83 (48.0%) were facing health-related problems which were referred for an unscheduled visit; three (1.7%) sought some type of guidance, only one regarding PrEP adherence; two (1.2%) were not using PrEP and were referred to a study discontinuation visit.

From 11,003 SMS with no reply, 1,093 contact attempts were required, as the participant did not answered for three consecutive weeks. Of these, 421 (38.5%) were successful and 672 (61.5%) unsuccessful, as the participants did not answer the phone. The reasons for not replying the SMS messages for three consecutive weeks were: difficulties to receive the messages (8.0%; 87/421); unwillingness to answer or forgot (7.3%; 80/421); no pre-paid credit (4.9%; 54/421); personal problems (4.1%; 45/ 421); difficulties to reply the messages (4.0%; 44/421); desire to withdraw the substudy (2.3%; 25/421); problems with the mobile phone device (1.6%; 18/421); had a scheduled visit for the next few days (1.6%; 18/421); lost or changed the mobile phone number (1.5%; 16/421); mobile phone in roaming mode (1.3%; 14/421); PrEP Brasil study discontinuation (0.8%; 9/421); problems with daily routine (0.5%; 5/421); health-related problems (0.4%; 4/421); one confirmed HIV seroconversion and one did not inform the reason.

Determination of the best MPR cutoff point for Adequate PrEP Aderence

During the PrEP Brasil study, 424 and 375 participants collected DBS samples (total of 799 samples) at weeks 4 and 48, respectively. Protective drug levels (TFV-DP ≥700 fmol/punch) corresponding to ≥4 doses/week were achieved for 78.5% at week 4 (24) and 74.0% at week 48 (28).

According to the ROC curve, MPR can predict protective drug levels measured by DBS (AUC 0.67 [95% CI:0.62-0.72]) with high sensitivity (Table 2). The calculated MPR cutoff point was 1.02, and individuals with MPR equal or superior to this value were considered with adequate PrEP adherence.

Adequate PrEP Adherence

Considering the average MPR values measured at weeks 4, 12, 24, 36, 48, a total of 404 individuals (76.4%) had adequate PrEP adherence across 48 weeks, 78.4% and 74.3% from SMS and SoC intervention arms, respectively. The proportion of individuals with adequate PrEP adherence was superior on SMS intervention arm compared to SoC across the study visits (p=0.04; Figure 3). In multivariable model, SMS intervention was a predictor of adequate PrEP adherence (AOR 1.37; CI 95%: 1.07-1.75) when adjusted by study visit, site location, age, condomless receptive anal sex and binge drinking (Table 3). Being from São Paulo (AOR= 1.42; CI 95%: 1.10-1.85) and having condomless receptive anal sex (AOR=1.40; CI 95%: 1.09-1.80) increased the odds of adequate PrEP adherence while being 18-24 years (AOR= 0.69; CI 95%: 0.48-0.99) and reporting binge drinking (AOR=0.72; CI 95%: 0.55-0.92) decreased the odds of adequate PrEP adherence.

Discussion

PrEP Brasil Study was the first demonstration project to explore the acceptability, safety and use of PrEP among MSM and TGW within the public health system in a middle income country. In the same sense, PrEP Brasil SMS Pilot Subst represents the first effort to develop a mHealth intervention to improve PrEP adherence among this population in Latin America.

Our study demonstrated that SMS intervention is effective to improve adequate PrEP adherence as measured by MPR. Studies have demonstrated that SMS can improve disease-related health outcomes (17), including ART adherence (29,30). Regarding the use SMS to improve PrEP adherence, the TAPIR Study, a randomized trial evaluating personalized daily text-messaging (iTAP) for PrEP adherence in the United States, demonstrated no difference between the study

arms for adequate adherence measured by drug levels (72.0% in iTAB and 69.2% in SoC; P > 0.05), but the intervention improved the durability of near-perfect PrEP adherence (33.5% vs 24.8%; P = 0.06), reaching statistical significance when adjusting for age (odds ratio, 1.56 [95% confidence interval, 1.00–2.42]; P < 0.05) (31). A youth-tailored multicomponent mHealth intervention grounded in the information, motivation, and behavioral (IMB) theory of behavior change (PrEPmate) significantly increased PrEP adherence measured by drug levels (72% PrEPmate vs. 57% SoC, OR = 2.05; 95% CI: 1.06-3.94) (32). The iPrEx Open-Label Pilot Substudy evaluating the use of a mobile health intervention (iText) demonstrated promising effects on PrEP adherence with 50% reduction on missed doses using clinic-based pill counts (95% CI: 16–71; p = 0.008) as well as increases of ∼28% in the MPR (p = 0.05) (22).

Younger age (18-24 years) and binge drinking were associated with lower PrEP adherence. Adherence to PrEP is challenging for young populations and tends to decline over time in this population (33–35). This is of concern as the number of new HIV infections is increasing among young MSM in Brazil (36). Conversely, younger age, binge drinking and condomless receptive anal sex were not associated with PrEP adherence in our previous analysis (24). This could be explained by methodological and study population differences. The former analysis was cross-sectional and considered PrEP adherence as having TFV-DP concentration ≥700 fmol/punch on DBS collected at week 48, while this was a longitudinal analysis considering all study visits. Although we have used an indirect methodology to access adherence (MPR), we have previously demonstrated that MPR is effective to discriminate individuals with and without protective drug levels at week 48 (27). Lastly, PrEP Brasil SMS Pilot Substudy study population differs from PrEP Brasil study as some participants did not agree to participate or were ineligible for the substudy (7.3%; 33/450).

Our study has provided evidence that a SMS intervention improved durability of PrEP coverage. Having MPR≥1 means that the participant received enough pills to take daily oral PrEP and, so s/he would be "covered" by FTC/TDF pills during all days between the study visits. Although only daily oral PrEP is recommended in Brazil (36), WHO has just published recommendations for event driven oral PrEP (ED-PrEP) among MSM (37). ED-PrEP will affect the way we interpret indirect adherence assessments (e.g. pill counts or MPR) as decisions on PrEP regimen and FTC/TDF pills consumption will depend on individuals' demands and choices based on HIV perceived risk and sexual behavior. In this sense, PrEP coverage is essential for effective daily oral PrEP or ED-PrEP and SMS can be a useful technology to prevent pill shortage.

The major strength of this study is the randomized clinical trial design, with allocation

concealment. The demographics and baseline characteristics of the study groups were well balanced and there was no significative difference in sample characteristics between intervention arms, and as such, less affected by selection or sampling bias. Although this was not a blinded study, the two main outcomes (TFV-DP level and MPR) are not liable to human interference. In addition, this was a low cost intervention as we can program the SMS platform to submit a large amount of text messages to different mobile phone numbers at the same time.

This study also has limitations. Although drug levels can be considered the gold standard for measuring adherence, we only collected DBS at weeks 4 and 48, avoiding the performance of longitudinal analysis considering all study visits. Nevertheless, we could demonstrate that MPR was an adequate adherence measurement.

Conclusion

In conclusion, a simple and low cost SMS-based intervention was effective to improve adequate PrEP adherence and can be a useful tool to prevent PrEP shortage. This is an example of how mHealth interventions can play an important role in addition to standard of care for PrEP use. Future interventions and web-based strategies to increase PrEP adherence among the youngest should be evaluated.

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Table 1. Baseline characteristics of participants enrolled in the PrEP Brasil SMS Pilot Substudy according to the intervention arm (SMS vs. SoC).

	SMS	SoC	Total	p-value
Total	207(49.6)	210(50.4)	417	
Site Location				0.98
Rio de Janeiro	85(49.7)	86(50.3)	171(41.0)	
São Paulo	122(49.6)	124(50.4)	246(59.0)	
Age (years)				0.07
18-24	60(58.8)	42(41.2)	102(24.5)	
25-35	90(44.8)	111(55.2)	201(48.2)	
>35	57(50.0)	57(50.0)	114(27.3)	
Schooling				0.76
<12 years	56(50.9)	54(49.1)	110(26.4)	
≥ 12 years	151(49.5)	156(50.8)	307(73.6)	
Color/Race				0.53
White	109(48.7)	115(51.3)	224(54.4)	
Black	23(44.2)	29(55.8)	52(12.6)	
Mixed	72(52.9)	64(47.1)	136(33.0)	
Gender				0.86
Cisgender men	195(49.7)	197(50.3)	392(94.0)	
Transgender women	12(48.0)	13(52.0)	25(6.0)	
Housing situation				0.16
Rent or own housing	125(47.0)	141(53.0)	266(63.8)	
Other (live with friends/family, live in public housing)	82(54.3)	69(45.7)	151(36.2)	
Steady partner				0.31
Yes	112(47.5)	124(52.5)	236(56.6)	
No	95(52.5)	86(47.5)	181(43.4)	
Sex with client				0.15
Yes	190(48.7)	200(51.3)	390(93.5)	
No	17(63.0)	10(37.0)	27(6.5)	
Condomless receptive anal sex				0.64
Yes	89(48.4)	95(51.6)	184(44.1)	
No	118(50.6)	115(49.4)	233(55.9)	
Sex with HIV+ partners				0.84
Yes	104(50.7)	101(49.3)	205(49.2)	
No	103(48.6)	109(51.4)	212(50.8)	
Binge drinking				0.56
Yes	127(50.8)	123(49.2)	250(60.0)	
No	80(47.9)	87(52.1)	167(40.0)	
Use of stimulants in last three months				0.76

Yes	38(48.1)	41(51.9)	79(18.9)	
No	169(50.0)	169(50.0)	338(81.1)	
Depression PHQ score				0.45
PHQ-2 score < 3	196(50.1)	195(49.9)	391(93.8)	
PHQ-2 score ≥ 3	11(42.3)	15(57.7)	26(6.2)	
STD diagnosis				0.69
Yes	39(47.6)	43(52.4)	82(19.7)	
No	168(50.1)	167(49.9)	335(80.3)	
GI symptoms				0.84
Yes	81(50.0)	81(50.0)	162(38.8)	
No	126(49.4)	129(50.6)	255(61.2)	

Table 2. Performance of MPR to predict protective drug levels measured by DBS and MPR cutoff point for Adequate PrEP Adherence.

	AUC (95% CI)	P-value	Cutoff point	Sensitivity	Specificity	PPV	NPV
MPR	0.67(0.62-0.72)	<0.0001	1.02	0.80	0.47	0.83	0.42

MPR= medication possession ratio; PPV = positive predictive value; NPV = negative predictive value.

Table 3. Factors Associated with Adequate PrEP Adherence. PrEP Brasil SMS Pilot Substudy.

	Number of participants[a,b]	Adequate PrEP Adherence[c] (%)	OR(95%CI)	p-value	AOR(95%CI)	p-value
Total	404	76.4				
SMS intervention						
Yes	200	78.4	1.24 (0.98-1.58)	0.07	**1.37 (1.07-1.75)**	**0.01**
No	204	74.3	Ref.			
Site Location						
Rio de Janeiro	165	71.0	Ref.			
São Paulo	239	80.0	1.64(1.29-2.08)	<0.0001	**1.42(1.10-1.85)**	**0.01**
Age (years)						
18-24	96	71.2	0.68(0.49-0.96)	0.03	**0.69(0.48-0.99)**	**0.04**
25-34	196	77.3	0.88(0.64-1.21)	0.43	0.92(0.67-1.26)	0.61
≥ 35	112	79.2	Ref.			
Schooling						
< 12 years	105	69.5	Ref.			
≥ 12 years	299	78.7	1.38(1.06-1.81)	0.02	1.28(0.96-1.72)	0.09
Color/Race						
White	216	76.7	Ref.			
Black	52	75.1	1.17(0.80-1.70)	0.41		
Mixed	131	75.6	1.10(0.83-1.46)	0.50		
Gender						
Cisgender men	379	76.9	Ref.			

Transgender women	25	67.9	0.74(0.47-1.17)	0.20		
Housing situation						
Rent or own housing	257	77.6	1.10(0.86-1.40)	0.44		
Other (live with friends/family, live in public housing)	140	74.8	Ref.			
Steady partner						
Yes	228	76.6	1.04(0.82-1.32)	0.72		
No	174	75.7	Ref.			
Sex with client						
Yes	25	68.7	0.67(0.43-1.06)	0.09	0.64(0.39-1.06)	0.08
No	377	76.5	Ref.			
Condomless receptive anal sex						
Yes	178	79.4	1.34(1.05-1.71)	0.02	**1.40(1.09-1.80)**	**0.01**
No	224	73.6	Ref.			
Sex with HIV+ partners						
Yes	201	77.5	1.02(0.80-1.31)	0.87		
No	187	76.3	Ref.			
Binge drinking						
Yes	236	73.8	0.72(0.56-0.93)	0.01	**0.72(0.55-0.92)**	**0.01**
No	166	80.1	Ref.			
Use of stimulants in last three months						
Yes	71	76.3	0.90(0.66-1.22)	0.50		

No	331	76.2	Ref.	
Depression PHQ score				
PHQ-2 score< 3	377	76.4	Ref.	
PHQ-2 score ≥ 3	26	75.0	0.96(0.63-1.47)	0.86
STD diagnosis				
Yes	77	78.1	1.14(0.83-1.57)	0.43
No	322	75.7	Ref.	
GI symptoms				
Yes	162	79.2	1.08(0.83-1.41)	0.56
No	230	75.6	Ref.	

a. analysis included 404 participants who had at least one visit during study follow-up; b. number of participants by characteristics is measured at week 4; c. indicates average prevalence of having mpr ≥ 1.02 across 48 weeks (the average of values measured at weeks 4, 12, 24, 36, 48); d) odds ratio adjusted for site and visit.

Figure 1. PrEP Brasil SMS Pilot Substudy Design Flowchart

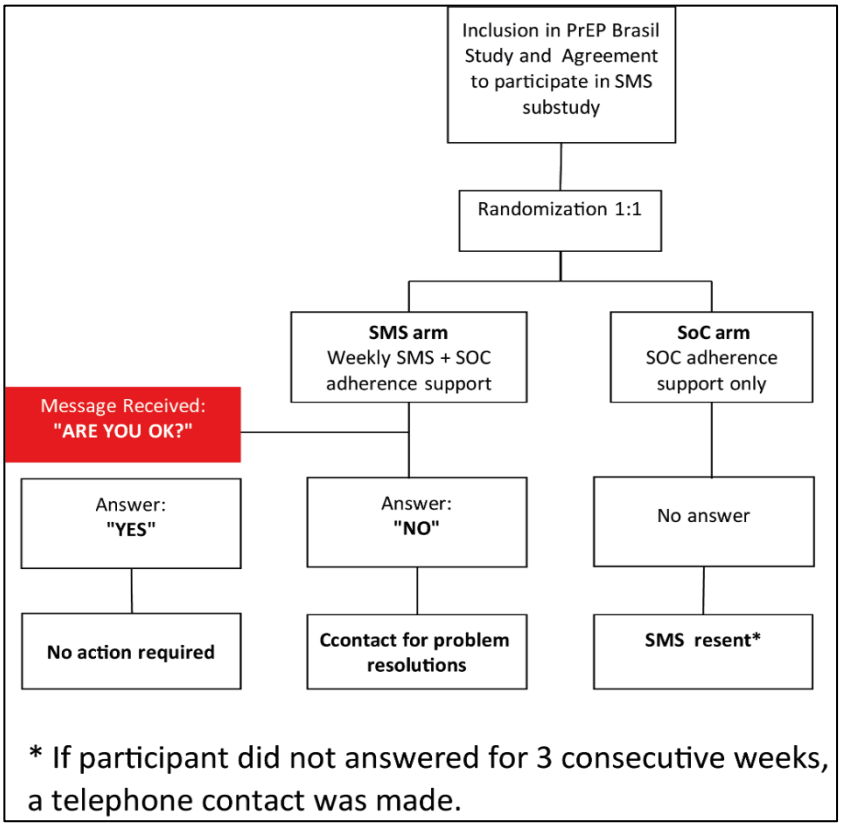


Figure 2. Consort Diagram, PrEP Brasil SMS Pilot Substudy.

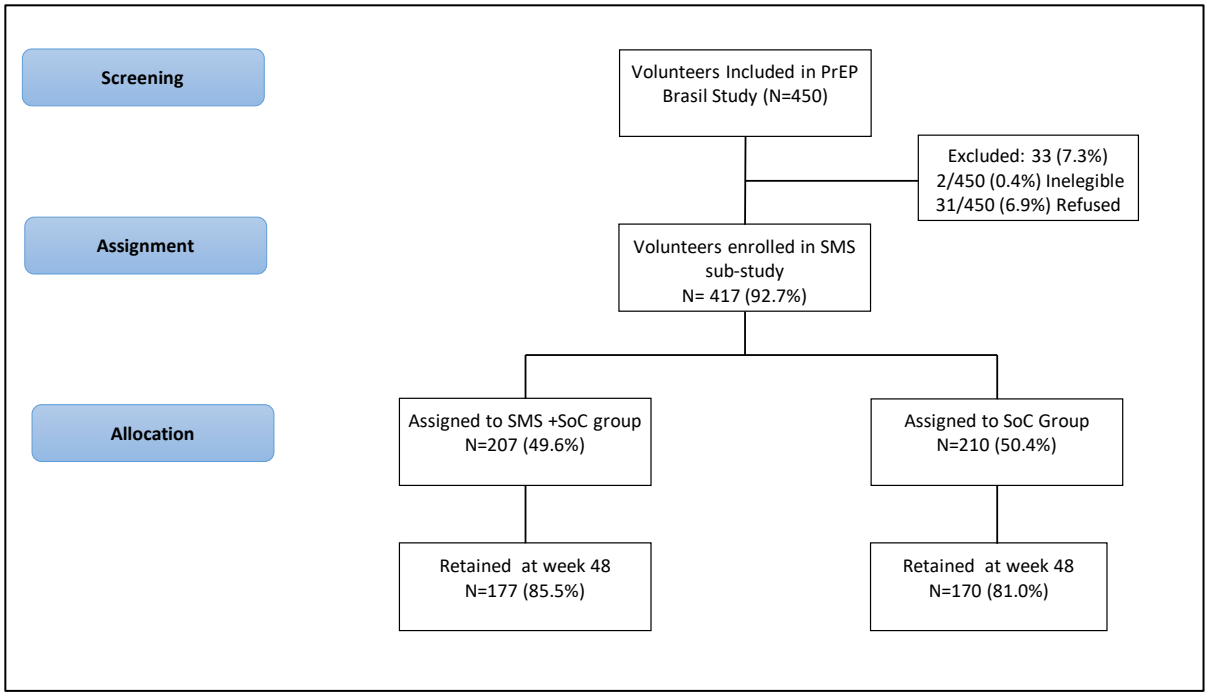
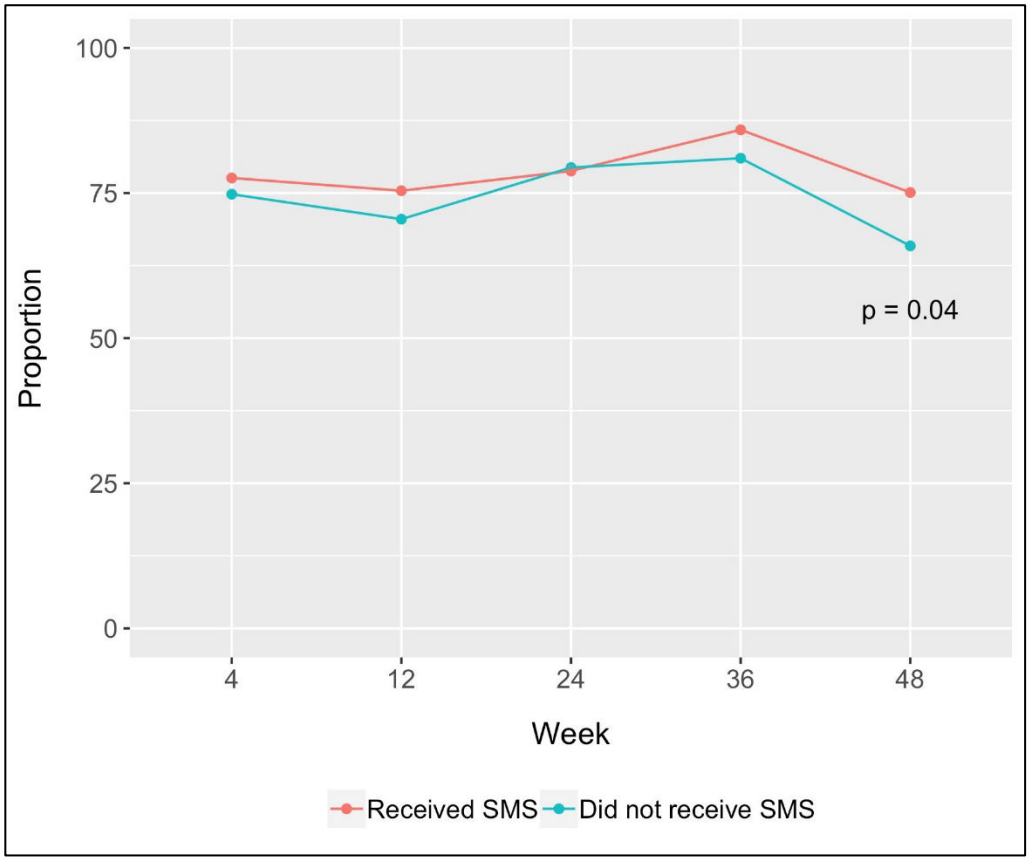


Figure 3. Proportion of participants with Adequate PrEP Adherence according to the intervention arm at each study visit, PrEP Brasil SMS Pilot Substudy.



7. TERCEIRO ARTIGO

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Predictors of self-reported adherence to PrEP, including perceived barriers and facilitators, among MSM and transgender women: PrEP Brasil Study

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Running head: Predictors of self-reported adherence to PrEP among MSM and trans women in Brazil

Predictors of self-reported adherence to PrEP, including perceived barriers and facilitators, among MSM and transgender women: PrEP Brasil Study

Abstract

Strategies for improving, supporting, motivating and sustaining adherence to PrEP are of great importance in maximizing its impact in high-risk populations. We evaluated self-reported adherence to daily oral PrEP (30 days-recall) and its perceived barriers and facilitators among men who have sex with men (MSM) and transgender women at week 48 of.PrEP Brasil study. We used logistic regression to evaluate predictors for optimal (=100%) adherence. From April/2014 to July/2016, 450 participants initiated PrEP, 375 (83.3%) were followed through 48 weeks. Of these, 354 (94.4%) received FTC/TDF in the previous 3 months and 338 (90.1%) answered the questionnaire. Median age was 30 years (IQR: 25-35). Median adherence in the past 30-days was 100% (IQR:92-100); 60.6% of participants (205/338) reported optimal adherence. The majority (82.2%; 278/338) of participants reported not having difficulty with taking FTC/TDF and 81.3% (274/338) reported excellent or very good capacity to take FTC/TDF in the past 30-days. Perceived barriers and facilitators to PrEP were reported by 38.2% and 98.5%, respectively. The main barriers to PrEP included forgetting doses (50%) and change in daily routine (38%), while the main facilitators included associating with some daily activity (59%) and being engaged with PrEP (49%). In multivariate analysis, being from Rio de Janeiro, transgender women, stimulant use and having perceived barriers to PrEP were associated with decreased odds of optimal adherence. Our findings provide information for elaboration, reinforcement and/or update of strategies to improve adherence, especially among transgender women and stimulant users, and for developing the best practices to promote PrEP adherence in our context. Interventions to reduce patient forgetfulness may be beneficial.

Key words: PrEP, Self-report adherence, Facilitators to PrEP, Barriers to PrEP

Background

Pre-exposure prophylaxis (PrEP) with emtricitabine / tenofovir disoproxil fumarate (FTC/TDF) is a biomedical intervention with proven efficacy to reduce HIV acquisition among gay, bisexual and other men who have sex with man (MSM), transgender women (TGW) and cisgender heterosexual couples (Grant et al., 2014a, 2010; McCormack et al., 2016; Molina et al., 2015; Thigpen et al., 2012). The efficacy of PrEP is highly dependent on adherence (Gandhi et al., 2015). Studies have well demonstrated the relationship between intake of FTC/TDF and protective efficacy (Anderson et al., 2012; Grant et al., 2014b, 2010; Marrazzo et al., 2015; Van Damme et al., 2012).

Accurate adherence measures play an import role in monitoring PrEP use in clinical practice (Liu et al., 2014). Despite drug levels measurement gives objective indication of drug ingestion, the high costs makes it not feasible for routine clinical practice (Haberer, 2016; Haberer et al., 2015). The most common approach to assess adherence for antiretroviral oral drugs is by individual's self-report (Amico, 2012; Costa, Torres, Coelho, & Luz, 2018). Self-report is recognized to overestimate adherence because of multiple bias albeit its readily and inexpensive method (Haberer, 2016). In iPrEX open label study, self-reported adherence measured through neutral interviewing was an useful tool to assess adherence in real-world in the absence of objective measures (Amico et al., 2016). In the TDF2 trial, self-reported adherence could predicted drug level in bivariate and controlled multivariate analyses (Kebaabetswe et al., 2015). Similarly, a previous exploratory study from our group had suggested that self-reported adherence could discriminate individuals with and without protective drug levels at week 48, being useful in monitoring PrEP use in PrEP Brasil study. We have also determined that 99.9% of self-report adherence corresponds to the best cutoff point to discriminate high levels of adherence (PPV= 0.84) ("Oral abstracts of the 22nd International AIDS Conference, 23-27 July 2018, Amsterdam, the Netherlands," 2018).

Understanding the factors associated with adherence to PrEP may help in the development of strategies to support, motivate and sustain PrEP use maximizing the impact of this technology in reducing HIV spread in high-risk populations (Baxi et al., 2015; Corneli et al., 2014; Mitchell et al., 2018). A recent systematic review has shown that adherence to oral PrEP varies substantially among trials and populations, and the main reasons of non-adherence were low HIV risk perception, side-effects, perceived stigma and dosing regimen incompatibility (Sidebottom, Ekström, & Strömdahl, 2018). Another recent systematic review identified barriers and facilitators to PrEP in social- media online posts that were not present in the peer-reviewed manuscripts. Some of the facilitators included "Doctors who are sensitive to race and poverty", "Effective even

with missed doses",“Can use PrEP only for high risk period", while the barriers included “Lack of access to healthcare", “Public has inadequate understanding of the science behind PrEP" and “Others assume promiscuity" (Hannaford et al., 2018). In an online survey among 19,457 MSM from Brazil, Mexico and Peru, the main facilitators to PrEP were PrEP at no cost, access to free HIV test, access to other free exams and access to personal PrEP counseling, while the main reported barriers were afraid of not being 100% protected against HIV, afraid of side effects and afraid that antiretroviral therapy (ART) would not work if getting infected (57.38%) (Torres et al., 2019).

This study aims to access the prevalence and predictors of self-reported adherence to daily oral PrEP, including barriers and facilitators, among MSM and TGW retained through 48 weeks in PrEP Brasil Study.

Methods

PrEP Brasil study

PrEP Brasil was a prospective, open-label demonstration study with HIV-uninfected MSM and TGW at higher risk for HIV infection from three referral centers for HIV treatment and prevention within the Brazilian Public Health System in Rio de Janeiro (INI-Fiocruz) and São Paulo (CRT-SP and USP). Participants were followed-up for 48 weeks and daily oral FTC/TDF was provided. Details of PrEP Brasil study methodology and main results were described elsewhere (Grinsztejn et al., 2018; Hoagland et al., 2017) .

Adherence outcomes

We included in this analysis participants who agreed to complete the questionnaire at week 48 of PrEP Brasil study and received FTC/TDF in the previous three months.

PrEP self-reported adherence, perceived barriers and facilitators for PrEP were assessed using a structured questionnaire. We used the following question to evaluate self-reported adherence: “How many days did you forget to take FTC/TDF in the previous 30 days?". We categorized the answers using the following timeframes: past week, 1-2 weeks and 3-4 weeks. We considered optimal self-reported adherence if the participant did not miss any dose in the past 30 days (cuf-off = 100%) (“Oral abstracts of the 22nd International AIDS Conference, 23-27 July 2018, Amsterdam, the Netherlands," 2018).

Perceived barriers and facilitators to PrEP adherence were assessed using the questions:

“In the previous 30 days have any of the following made difficult (or easier, for facilitators) taking PrEP?”; pre-established answers were provided and more than one reason could be chosen. Difficulty to take daily oral FTC/TDF was assessed by the question: “Thinking about the previous 30 days, how many times have you felt you had difficult to use FTC/TDF?”; pre-established answers were provided (never, rarely, sometimes, often, always and do not want to answer) and only one answer could be chosen. The ability to take daily FTC/TDF in the previous 30 days was assessed by the question: "Please rate your ability to take FTC/TDF daily in the previous 30 days:"; pre-established answers were provided (very bad; bad; neutral, good, very good, excellent and do not want to answer) and only one answer could be chosen.

Statistical analysis

We used chi-square or Fisher’s exact test to compare the baseline characteristics of participants included in this analysis vs. those not included. We compared the main outcome (optimal self-reported adherence) by participant characteristics using chi-square tests to evaluate differences. We explored the predictors for optimal self-reported adherence using logistic regression models. Only variables with $p<0.10$ after adjusting for site location (Rio de Janeiro or São Paulo) were kept in the final adjusted model (adjusted odds ratio – AOR).

Ethical Considerations

As previous described (Grinsztejn et al., 2018; Hoagland et al., 2017), Institutional review boards (IRB) at the three referral centers approved PrEP Brasil study. All study participants signed an informed consent form at prescreening and screening visits. The study was done according to the principles expressed in the Declaration of Helsinki and this analysis was approved by INI-Fiocruz IRB (#08405912.9.1001.5262).

Results

From April/2014 to July/2016, 450 participants initiated PrEP; 375 (83.3%) were retained at 48 weeks and 354 (94.4%) received FTC/TDF pills in the previous three months. Of these, 338 (90.1%) completed the questionnaire at week 48 and were included in this analysis. Median age was 30 years (IQR: 25-35). Table 1 provides baseline characteristics of participants included (n=338) vs. not included in this analysis (n=112). More individuals from Rio de Janeiro, younger age (18-24 years), less years of schooling (<12 years) and non-white were not included in comparison to those included.

Median self-reported adherence in the recall time frame of 30-days was 100% (IQR:92-100). A total of 60.6% (205/338) participants reported not missing any dose of FTC/TDF (optimal

self-reported adherence); 8.0% (27/338), 15.1% (51/338) and 15.7% (53/338) reported missed doses in the past week, 1-2 weeks and 3-4 weeks, respectively and 0,6% (2/338) did not want to inform when was the last forgotten dose.

A total of 38.2% (129/338) participants reported one or more perceived barrier to PrEP adherence, while 98.5% (333/338) reported perceived facilitators to PrEP adherence. Perceived barriers and facilitators to PrEP adherence are depicted in Table 2 and Table 3, respectively. The main barriers to PrEP included forgetting doses (50%), change in daily rotine (38%), pills shortage (25%) and not having pills available at the time of dose (12%). Barriers related to drug or alcohol use, no HIV perceived risk, privacy issues or side effects were uncommon (≤10%). The main facilitators included associating with some daily activity (59%), being engaged with PrEP (49%), keeping the tablets in a visible place and carrying the medication with oneself (45%), use of alarm (39%), fear of getting HIV infected (38%), associating with another medication (16%) and being helped by someone (11%).

The majority (82.2%; 278/338) of participants reported not having any difficulty when taking FTC/TDF and 81.3% (274/338) reported excellent or very good ability to take FTC/TDF in the past 30-days.

In final multivariate logistic analysis, being from Rio de Janeiro, TGW, stimulant use and having any perceived barriers to PrEP adherence were associated with decreased odds of optimal adherence, as presented in Table 4.

Discussion

The purpose of this study was to estimate self-reported optimal adherence and to investigate perceived barriers and facilitators to PrEP adherence among MSM and TGW in the context of a public health program in a middle-income country. Our findings can be suitably exploited in designing strategies to strengthen adherence and overcoming challenges on PrEP use in clinical practice.

We detected high levels of optimal self-reported adherence in the previous 30 days after one year of daily oral PrEP provision. This is consistent with our previous report that showed high adherence at week 48 measured by tenofovir-diphosphate (TFV-DP) levels (Grinsztejn et al., 2018) and also consistent with findings from open-label and demonstration projects either when measured by TFV-DP levels (Haberer, 2016; Liu et al., 2016; Montgomery et al., 2016; Musinguzi et al., 2016) or when accessed by self-report or pill count (Amico, 2012; Haberer et al., 2013).

Perceived barriers to PrEP adherence were less reported than facilitators (38.2% and 98.5%, respectively). This is consistent with the results of iPrEX open-label study; after reviewing

15,584 adherence counseling records of 1,947 participants, barriers and facilitators were identified in 32% and 96% of the assessments, respectively (R. Amico et al., 2012).

Similar to our results, change in daily routine (14%) and forgetting/memory (12%) were also the most reported barriers in iPrEX-OLE Study and drug or alcohol use, no HIV perceived risk, privacy issues or side effects were also uncommon (≤5%) (R. Amico et al., 2012). In the same sense, a qualitative study within a group of participants of the randomized double-blinded iPrEX study participants in San Francisco identified that changes in routine influenced pill use and adherence (Gilmore et al., 2013). An observational study within the context of the open-label PrEP study ATN110/113 also found forgetting doses or not available doses (13.6%) and disrupting in routine (27.0%) as barriers to PrEP adherence (Amico et al., 2018). Simply forgetting doses (28.5%) was also the most common overall reasons reported by participants for missing study pills in a PrEP open label demonstration study among young MSM aged 18–22 (ATN 110 - Project PrEPare 2) (Hosek et al., 2017). Other barriers to PrEP adherence identified in different trials include heavy alcohol use, stigma, missing clinic visits, side effects, social stigma and stress (Blashill, Ehlinger, Mayer, & Safren, 2015; Gilmore et al., 2013; Taylor et al., 2017). In our study, alcohol use, privacy to take pills, ranning out of pills, side effect, sadness, anger or anxious were not perceived barriers for PrEP adherence. Additionally, it is important to understand and develop strategies to minimize the levels of dose forgetfulness. Furthermore, an accurate recall of missed doses can minimize forgetfulness bias allowing individuals with low self-reported adherence to be easily assessed to receive adherence support and counseling, as well as to be guided for the adoption of other risk reduction methods within the strategies of combined prevention.

Our findings on facilitators to PrEP adherence were also similar to other studies. iPrEX-OLE, identified that the most frequently reported facilitator was the incorporation of study product into daily routine (82%), followed by the use of a memory aid like (21%) (R. Amico et al., 2012). The observational study within ATN110/113 also found that match PrEP use with a routine (37.78%), commitment or protecting self or other (28.81%, carring tools (82.85%), social support (16.82%) were facilitators of PrEP use (Amico et al., 2018). Our results suggest that, motivational and behavioral skills like being engaged with PrEP use, associate with routine and carrying pills, may facilitate adherence and this can be used to improve and/or reinforce adherence in our population.

Stimulant use was associated with decreased odds of optimal adherence. This is consistent with previous studies results. iPrEX OLE demonstrated that cocaine use (a stimulant) was associated with greater odds of non-adherence measured by drug levels (Hojilla et al., 2019). In a observational study assessing PrEP use after 48 weeks of participation in a randomized controlled trial, the only significant predictor of self-reported linkage to PrEP was less problematic substance

use (OR per DAST10 score point 0.757, 95%CI 0.595 – 0.962; p=0.023) (Hoenigl et al., 2019). Decreased odds of self-reported optimal adherence was also found within the TGW participants. A similar pattern was found in a demonstration project assessing retention and adherence among HIV-uninfected Thai MSM and TGW (aOR: 2.2, 95% CI: 1.27–3.83, p = 0.005) (Seekaew et al., 2019). TGW have unique life contexts, being in disadvantaged and disenfranchised group, with multiple needs (Garcia Ferreira et al., 2019) which may explain the low PrEP self-report adherence within this group. A better understanding of TGW and stimulant users' needs and implications on adherence and developing the best practices to promote PrEP adherence is required. A PrEP demonstration project specifically designed for transwomen (PrEParadas) is ongoing in Brazil and hopefully more information about barriers and facilitators for PrEP among this population will be available soon ("Oral abstracts of the 10th IAS Conference on HIV Science, 21-24 July 2019, Mexico City, Mexico," 2019).

Unlike seen in our previous analysis, age, sex with HIV positive partners and TGW did not demonstrate a statistically significant effect on TFV-DP levels, while stimulant use had increased odds of achieving protective levels at week 48 of PrEP Brasil study (Grinsztejn et al., 2018). These divergences between our two analyses may be explained by the definition of adherence. Here, we considered as optimal self-reported adherence if the participant did not miss any dose in the past month (SR = 100%), while for the previous analysis only 4 doses/week were enough to achieve adherence.

The major limitation of our study is the assessment of adherence by self-report. Although self-reported adherence can be limited by different bias and may overestimate adherence (Baxi et al., 2015; Haberer, 2016), neutral assessment can minimize "social desirability bias" being recommended to ensure the quality standard in use of self-report (Amico, 2012; Amico et al., 2014). Additionally, we have previous demonstrated that self-report could discriminate PrEP Brasil participants with and without protective drug levels at week 48 in a public health context in Brazil (AUC 0.65; [95% CI 0.58-0.72]; PPV= 0.84) ("Oral abstracts of the 22nd International AIDS Conference, 23-27 July 2018, Amsterdam, the Netherlands," 2018). Strong correlation between self-report adherence and drug levels was also found in a clinical setting PrEP program study (Montgomery et al., 2016), suggesting that self-report can be used to predict PrEP adherence. Another important limitation is the significative differences on baseline characteristics between participants included and not included in this analysis. More participants from Rio de Janeiro site, younger age (18-24 years), less years of schooling (<12 years) and non-white missed week 36 and thus, they were not "covered" by the study medication for the current approved recommendation of daily PrEP. Thus, our data may be affected by selection or sampling bias.

Conclusions

High levels of self-reported adherence were reported among MSM and TGW retained through 48 weeks in the PrEP Brasil study. Our findings provide information for elaboration, reinforcement and/or update of strategies to improve adherence and for developing the best practices to promote PrEP adherence in our context. Implementation of motivational and behavior improvement strategies and interventions to reduce patient forgetfulness may be beneficial.

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Table 1: Baseline characteristics of participants included vs. not included in this analysis. PrEP Brasil study.

	Included	Not included	Total initiating PrEP Brasil	p-value[a]
Overall	338 (75.1%)	112 (24.9%)	450	0.23
Site Location				
São Paulo	220 (65.1%)	50 (44.6%)	270	<0.01
Rio de Janeiro	118 (34.9%)	62 (55.4%)	180	
Age				
18-24 years	75 (22.2%)	38 (33.9%)	113	0.04
25-34 years	169 (50.0%)	45 (40.2%)	214	
≥35 years	94 (27.8%)	29 (25.9%)	123	
Schooling				
< 12 years	73 (21.6%)	42 (37.5%)	115	0.01
≥ 12 years	265 (78.4%)	70 (62.5%)	335	
Color/Race				
White	192 (57.5%)	51 (45.9%)	243	0.03
Non-white	142 (42.5%)	61 (54.1%)	202	
Gender				
Cisgender Male	320 (94.7%)	105 (93.8%)	425	0.81
Transgender women	18 (5.3%)	7 (6.2%)	25	
Housing situation				
Rent or own	222 (66.5%)	67 (61.5%)	289	0.34
Other	112 (33.5%)	42 (38.5%)	154	
Steady partner				
Yes	195 (57.7%)	59 (52.7%)	254	0.35
No	143 (42.3%)	53 (47.3%)	196	
Had sex with client[b]				
Yes	17 (5.0%)	10 (8.9%)	27	0.13
No			423	
Condomless receptive anal intercourse[b]				
Yes	159 (47.0%)	42 (37.5%)	201	0.08
No	179 (53.0%)	112 (62.5%)	249	
Sex with HIV positive partners[b]				
Yes	173 (52.7%)	50 (46.7%)	223	0.28
No	155 (47.3%)	57 (53.3%)	212	
Binge drinking[b]				
Yes	200 (59.2%)	66 (58.9%)	266	0.96
No	138 (40.8%)	46 (41.1%)	184	
Stimulants Use[b, c]				
Yes	68 (20.1%)	23 (20.5%)	91	0.92
No	270 (79.9%)	89 (79.5%)	359	
Depression PHQ score[d]				
PHQ-2 score ≥ 3	20 (5.9%)	7 (6.3%)	27	0.88

PHQ-2 score < 3	318 (94.1%)	104 (93.7%)	422	
STD diagnoses[b, e]				
Yes	67 (21.9%)	22 (13.9%)	89	0.90
No	239 (78.1%)	136 (84.1%)	355	
GI symptoms[f]				
Yes	140 (42.2%)	38 (41.3%)	178	0.88
No	192 (57.8%)	54 (58.7%)	246	
Received text message[g]				
Yes	161(47.6%)	46(41.1%)	207	0.24
No	177 (52,4%)	66 (58.9%)	243	

a) Chi-square or Fisher's exact test;
b) previous 3 months;
c) powder cocaine, crack, amphetamines or club drugs (ecstasy, LSD, ketamine, GHB);
d) Patient Health Questionnaire-2 (PHQ-2) ≥3.
e) any positive laboratorial diagnosis for syphilis, gonorrhea or chlamydia at screening/enrollment.
f) abdominal pain, diarrhea, flatulence, nausea and vomiting
g) Participants who agreed to participate (94%) were randomly allocated to receive or not receive text messages (SMS); those who chose not to participate (n=29) were categorized as "No".

Table 2. Perceived Barriers to PrEP Adherence, PrEP Brasil study.

Barriers	N (%)
I forgot to take my pills	65/338 (19.2)
I have changed my planned schedule	49/338 (14.5)
I didn't had my pills with me	32/338 (9.5)
Ran out of pills	15/338 (4.4)
I have drank or got high	13/338 (3.9)
I felt I had no risk or low risk of getting HIV	8/338 (2.4)
I wanted to take the pills with privacy	7/338 (2.1)
I felt sadness, anger or anxious	6/338 (1.8)
I have planned to drink or become high	4/338 (1.2)
I had my pills stolen	1/338 (0.3)
I did not want to take the pills with me	1/338 (0.3)
I had a side effect or was feeling bad	1/338 (0.3)

Table 3. Perceived Facilitators to PrEP Adherence. PrEP Brasil study.

Facilitators	N (%)
Associate PrEP with a daily activity or task	198/338 (58.6)
Felt really engaged on taking PrEP	164/338 (48.5)
Taking pills with me	149/338 (44.1)
Keep pills under sight	151/338 (44.7)
Mobile phone alarm	130/338 (38.5)
Worried with HIV infection	126/338 (37.3)
Associate taking PrEP with concomitant drug	52/338 (15.4)
Being helped by someone	37/338 (10.9)

Table 4. Predictors of optimal self-reported adherence (100%) at week 48. PrEP Brasil study.

	Optimal adherence (100%) n (%)	OR (95%CI)[a]	p-value	AOR (95%CI)	p-value
Overall	205(60.6)				
Site Location					**0.004**
São Paulo	150(68.2)	Ref.		Ref.	
Rio de Janeiro	55(46.6)	0.41(0.26-0.64)	<.001	0.38(0.20-0.73)	
Age					
18-24 years	43(57.3)	0.71(0.37-1.35)	0.30	b	
25-34 years	99(58.6)	0.68(0.40-1.17)	0.16	b	
≥35 years	63(67.0)	Ref.		b	
Schooling					
< 12 years	45(61.6)	Ref.		b	
≥ 12 years	160(60.4)	0.66(0.37-1.18)	0.16	b	
Color/Race					
White	118(61.5)	Ref.		b	
Non-white	83(58.5)	1.20(0.74-1.94)	0.47	b	
Gender					
Male	199(62.2)	Ref.		Ref.	
Transwomen	6(33.3)	0.41(0.14-1.14)	0.09	0.22(0.07-0.73)	**0.01**
Housing situation					
Rent or own	139(62.6)	1.18(0.73-1.90)	0.49	b	
Other[c]	63(56.2)	Ref.		b	
Steady partner					
Yes	118(63.8)	1.30(0.83-2.04)	0.25	b	
No	87(56.9)	Ref.		b	
Had sex with client[d]					
Yes	5(62.5)	1.12(0.25-4.91)	0.89	b	
No	200(60.6)	Ref.		b	
Condomless receptive anal intercourse[d]					
Yes	100(59.9)	0.85(0.54-1.33)	0.48	b	
No	105(61.4)	Ref.		b	
Sex with HIV positive partners[d]					
Yes	93(66.4)	1.46(0.92-2.32)	0.10	0.90(0.92-2.44)	0.75
No	112(56.6)	Ref.		Ref.	
Binge drinking[d]					
Yes	126(57.8)	0.72(0.45-1.16)	0.18	b	
No	79(65.8)	Ref.		b	
Stimulants[d]					
Yes	40(54.8)	0.58(0.33-1.00)	0.05	0.40(0.20-	**0.01**

				0.80)	
No	165(62.3)	Ref.		Ref.	
Depression PHQ-2 score					
< 3	197(62.0)	Ref.		Ref.	
≥ 3	8(40.0)	0.39(0.15-1.01)	0.05	0.41(0.14-1.22)	0.11
STD diagnosis[e]					
Yes	39(65.0)	1.29(0.71-2.34)	0.40	b	
No	166(59.7)	Ref.		b	
GI symptoms[f]					
Yes	83(59.3)	0.64(0.39-1.05)	0.08	1.02(0.54-1.93)	0.95
No	119(62.0)	Ref.		Ref.	
Received text message[g]					
Yes	95(59.0)	0.84(0.54-1.31)	0.45		
No	110(62.1)	Ref.			
Any Perceived barrier to PrEP					
Yes	35(27.1)	0.09(0.05-0.15)	<.001	0.12(0.07-0.23)	**<.001**
No	170(81.3)	Ref.		Ref.	

a) Odds ratio adjusted for site location only
b) Not included in final adjusted models.
c) Includes living with friends/family or in public housing
d) In the previous three months
e) Includes rectal chlamydia, rectal gonorrhea, or syphilis
f) Any among the following: abdominal pain, diarrzhoea, flatulence, nausea and vomiting
g) Participants who agreed to participate (93.5%) were randomly allocated to receive or not text messages; those who chose not to participate (n=29) were categorized as No.

8. CONCLUSÕES

- Altos níveis de adesão mensurados por diferentes métodos indiretos (contagem de comprimidos, MPR e autorrelato) foram verificados na semana 48.
- Todos os métodos indiretos de adesão foram capazes de discriminar participantes que atingiram ou não níveis protetores de tenofovir.
- Nosso estudo foi capaz de determinar os melhores pontos de corte para discriminar altos níveis de adesão.
- Altos níveis de adesão foram preditivos de níveis protetores de TVF-DP, porém baixos níveis de adesão não foram preditivos de níveis não protetores.
- A intervenção por SMS foi eficaz para melhorar a adesão e a cobertura de PrEP ao longo do estudo, mas não teve impacto na retenção na semana 48.
- As principais barreiras à PrEP foram esquecimento e mudança na rotina diária, enquanto que os principais facilitadores foram associar a PrEP a alguma atividade diária e estar engajado(a) no uso da PrEP.
- Participantes do Rio de Janeiro, TrMT, uso de estimulante e ter alguma barreira à PrEP foram preditores de baixa adesão autorrelatada de PrEP.

9. RECOMENDAÇÕES E DESDOBRAMENTOS

1. Nossos resultados destacam a utilidade de medidas acessíveis de adesão como MPR e autorrelato no monitoramento do uso da PrEP e na orientação da necessidade de intervenções de adesão em programas de PrEP.
2. O SICLOM pode ser utilizado como uma fonte de dados única para a avaliação da adesão (MPR) no SUS.
3. O uso de duas ou mais medidas de adesão pode ser útil para identificar mais eficientemente a baixa adesão no "mundo real". Estudos sobre o valor incremental da combinação de MPR e autorrelato na previsão da adesão entre nossa população-alvo são necessários.
4. Estudos utilizando mensagens por WhatsApp ou outros aplicativos deveriam ser implementados para aumentar a adesão e cobertura da PrEP entre os mais jovens.
5. SMS pode ser um método útil para melhorar a cobertura de FTC/TDF e prevenir a baixa adesão, uma vez que os indivíduos podem tomar decisões sobre o uso da PrEP com base em seu comportamento de risco e ter comprimidos de FTC/TDF disponíveis é uma condição necessária para garantir a efetividade da PrEP,

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11. ANEXOS

ANEXO 1: Carta de Aprovação do CEP INI-FIOCRUZ para o Projeto PrEP Brasil

ANEXO 2: Carta de Aprovação do CEP INI-FIOCRUZ para a Emenda ao Projeto PrEP Brasil

ANEXO 3: E-mail de confirmação de aceite da publicação do primeiro artigo

ANEXO 1: Carta de Aprovação do CEP INI-FIOCRUZ para o Projeto PrEP Brasil

INSTITUTO DE PESQUISA CLÍNICA EVANDRO CHAGAS - IPEC / FIOCRUZ

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: IMPLEMENTAÇÃO DA PROFILAXIA PRÉ-EXPOSIÇÃO (PrEP) AO HIV: UM PROJETO DEMONSTRATIVO

Pesquisador: Beatriz Grinsztejn

Área Temática:

Versão: 2

CAAE: 08405912.9.1001.5262

Instituição Proponente: Instituto de Pesquisa Clínica Evandro Chagas - IPEC / FIOCRUZ

DADOS DO PARECER

Número do Parecer: 156.320

Data da Relatoria: 26/11/2012

Apresentação do Projeto:

Protocolo Versão 1.1, de 22/11/2012. Os resultados iniciais dos ensaios clínicos de quimioprofilaxia pré-exposição (PrEP), sob a forma de uma pílula por via oral (PrEP oral) indicam que essa estratégia pode ser extremamente útil para a mudança de cenário necessária na luta contra a infecção pelo HIV. A PrEP se baseia no uso de medicamentos antirretrovirais (ARV) para a prevenção da aquisição do HIV e sua eficácia parcial foi demonstrada entre homens que fazem sexo com homens (HSH) e heterossexuais. Intervenções de prevenção biomédica, como a PrEP, têm um grande potencial, especialmente se combinadas a testagem anti-HIV ampliada, diagnóstico e vinculação ao tratamento daqueles identificados como infectados pelo HIV. HIV/AIDS é uma das maiores pandemias já enfrentada pela humanidade, estimando-se haver atualmente mais de 30 milhões de pessoas vivendo com HIV/AIDS em todo o mundo. Várias linhas de evidências sugerem que os atuais programas de testagem e tratamento do HIV não são ideais para reduzir com eficácia a transmissão do vírus. Em uma epidemia concentrada, o HIV se espalha rapidamente em uma ou mais subpopulações específicas, com propagação relativamente modesta na população geral. Nestes contextos, as redes de populações de risco têm um papel preponderante na dinâmica da epidemia. A maioria de países da América Latina foi afetada por epidemias concentradas de HIV/AIDS e as taxas de infecção pelo HIV nesta região mudaram pouco na década passada. A transmissão do HIV ocorre principalmente entre os homens que fazem sexo com homens (HSH), que são desproporcionalmente afetados pelo HIV/AIDS globalmente, tendência que está se tornando mais forte nos últimos anos. Estratégias seguras e eficazes de prevenção do HIV

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dirigidas a esta população são necessárias com urgência. O Brasil, com uma população de aproximadamente 180 milhões, ocupa o segundo lugar nas Américas em número de casos de AIDS notificados. Após 30 anos, o Brasil apresenta uma epidemia que pode ser caracterizada como estável e concentrada em subgrupos com maior vulnerabilidade. A profilaxia pré-exposição (PrEP) para prevenção do HIV tem demonstrado eficácia parcial com homens que fazem sexo com homens (HSH) e heterossexuais. A Organização Mundial da Saúde (OMS) afirma que a PrEP pode ser priorizada para populações de maior risco incluindo HSH, UDI e profissionais do sexo, bem como para "todos aqueles em risco de transmissão sexual em áreas com transmissão endêmica ou hiperendêmica do HIV, tais como a África de Sul". Em julho de 2012 foram divulgadas as medidas diretivas da Organização Mundial de Saúde (OMS) sobre o uso de PrEP, recomendando seu uso para as populações mais vulneráveis, entre elas os HSH. A OMS também enfaticamente recomenda que os países desenvolvam estudos de demonstração da implementação dessa estratégia de prevenção a fim de que possam ser identificados e adequadamente encaminhados os problemas para a implementação dessas estratégias em larga escala. Os dados produzidos a partir de estudos de demonstração como esse irão subsidiar as ações para a introdução da PrEP nos programas de prevenção do HIV, tanto nos países de alta prevalência como nas epidemias concentradas como as que afetam os HSH em muitos países tais como o Brasil. O presente estudo consiste de um projeto demonstrativo prospectivo não controlado conduzido em três centros de estudo, que visa avaliar a absorção, aceitação, segurança e viabilidade da PrEP diária entre HSH e mulheres transexuais. Cada participante irá receber PrEP por até um ano. Além da PrEP, os participantes receberão um pacote completo de serviços de prevenção ao HIV, que inclui preservativos e aconselhamentos de redução de risco. Os participantes serão monitorados trimestralmente para avaliação de efeitos colaterais, toxicidade renal, adesão, comportamento de risco e soroconversão para HIV.

Objetivo da Pesquisa:

Objetivo Primário: 1) Descrever a aceitação da PrEP diária oferecida a HSH e mulheres transexuais; 2) Determinar a diferença na aceitação da PrEP diária de acordo com características sócio-demográficas, incluindo raça/etnia, idade, escolaridade e práticas de risco; 3) Determinar a diferença na duração do uso da PrEP de acordo com características sócio-demográficas, incluindo raça/etnia, idade, escolaridade e práticas de risco; 4) Descrever os efeitos colaterais e toxicidade da PrEP entre os participantes; 5) Descrever padrões e correlações da adesão à PrEP entre os participantes; 6) Mensurar as mudanças no comportamento sexual de risco entre os participantes. Objetivo Secundário: 1) Descrever o conhecimento da PrEP entre HSH e mulheres transexuais; 2) Descrever os motivos que levam à escolha de iniciar ou recusar a PrEP

oferecida a HSH e mulheres transexuais; 3) Descrever o número de soroconversões na coorte de participantes usando PrEP; 4) Descrever os padrões de resistência de medicamentos contra HIV entre pessoas que se tornem infectadas pelo HIV durante a participação no projeto demonstrativo de PrEP; 5) Avaliar o auto-relato de desvios (venda ou partilha) da PrEP; 6) Determinar as necessidades de espaço e equipe para administrar a PrEP no nosso meio; 7) Descrever os possíveis danos sociais decorrentes do uso de PrEP;

Avaliação dos Riscos e Benefícios:

Riscos: Os possíveis efeitos colaterais da PrEP incluem insuficiência renal, perda de densidade óssea, desconforto gastrointestinal, e piora da hepatite B crônica após a suspensão do uso. Dados sobre os efeitos a longo prazo do uso do tenofovir são ainda limitada. Além disso, muitos dos efeitos adversos são resultado do uso a longo prazo dessa medicação. O uso de longo prazo de PrEP não está estabelecido e muitos podem usá-la apenas temporariamente, por períodos limitados durante os momentos de maior risco. Se a PrEP intermitente for considerada eficaz, seus efeitos tóxicos podem ser minimizados. Forum for Collaborative HIV Research revisou cinco ensaios clínicos envolvendo mais de 6.000 e concluiu que "os efeitos adversos clínicos, incluindo outros efeitos adversos graves, tais como eventos gastrintestinais, náuseas, perda de peso e diarreia nos primeiros estágios da terapia, não parecem ser diferentes entre os grupos que receberam placebo ou medicamentos do estudo e são semelhantes aos eventos identificados com o uso de TDF e TDF/FTC em pacientes infectados pelo HIV." É importante que as pessoas que usam antirretrovirais para PrEP sejam plenamente informadas dos potenciais riscos e efeitos colaterais e que sejam acompanhadas de perto. Enquanto os antirretrovirais podem ter efeitos colaterais, o HIV também é uma doença grave. Pessoas com alto risco para o HIV que estão considerando usar PrEP devem pesar os potenciais custos e benefícios com os seus médicos e tomar uma decisão esclarecida se devem usar antirretrovirais para PrEP.

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 de relevância para a clínica.

Considerações sobre os Termos de apresentação obrigatória:

Os termos estão adequados ao que se propõem:

- Fluxo de testagem para o HIV - Versão do Protocolo 1.0 de 19/09/2012;

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- Termo de Consentimento Livre e Esclarecido - Versão 1.0 de 19/09/2012.

Recomendações:

Se possível, incluir o cronograma relacionado ao projeto no Protocolo Clínico.

Conclusões ou Pendências e Lista de Inadequações:

Todas as pendências foram adequadamente atendidas.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Este projeto foi apreciado e aprovado em reunião de 26 de novembro de 2012.

RIO DE JANEIRO, 28 de Novembro de 2012

Léa Camillo Coura

Assinador por:
Léa Ferreira Camillo-Coura
(Coordenador)

Endereço: Avenida Brasil 4365
Bairro: Manguinhos **CEP:** 21.045-900
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ANEXO 2: Carta de Aprovação do CEP INI-FIOCRUZ para a Emenda ao Projeto PrEP Brasil

INSTITUTO DE PESQUISA CLÍNICA EVANDRO CHAGAS - IPEC / FIOCRUZ

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: IMPLEMENTAÇÃO DA PROFILAXIA PRÉ-EXPOSIÇÃO (PrEP) AO HIV: UM PROJETO DEMONSTRATIVO

Pesquisador: Beatriz Grinsztejn

Área Temática:

Versão: 3

CAAE: 08405912.9.1001.5262

Instituição Proponente: Instituto de Pesquisa Clínica Evandro Chagas - IPEC / FIOCRUZ

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 467.987

Data da Relatoria: 11/11/2013

Apresentação do Projeto:

Protocolo versão 2.0 de 5 de setembro de 2013. Trata-se de uma EMENDA que visa a incluir novos membros da equipe, aumentar o número de participantes do estudo, incluir novos itens no procedimento do estudo (monitoramento dos níveis séricos de tenofovir, mensagens interativas para apoio ao uso dos comprimidos, sindemia, CASI, carga viral em pool), acrescentar objetivos secundários e desfechos secundários.

Objetivo da Pesquisa:

Objetivo Primário:

-Descrever a aceitação da PrEP diária oferecida a HSH e mulheres transexuais. -Determinar a diferença na aceitação da PrEP diária de acordo com características sócio-demográficas, incluindo raça/etnia, idade, escolaridade e práticas de risco. -Determinar a diferença na duração do uso da PrEP de acordo com características sócio-demográficas, incluindo raça/etnia, idade, escolaridade e práticas de risco. -Descrever os efeitos colaterais e

toxicidade da PrEP entre os participantes. -Descrever padrões e correlações da adesão à PrEP entre os participantes. -Mensurar as mudanças no comportamento sexual de risco entre os participantes.

Objetivo Secundário:

Endereço: Avenida Brasil 4365
Bairro: Manguinhos **CEP:** 21.045-900
UF: RJ **Município:** RIO DE JANEIRO
Telefone: (21)3865-9585 **E-mail:** cep@ipec.fiocruz.br

- Antes da EMENDA: 1) Descrever o conhecimento da PrEP entre HSH e mulheres transexuais. 2) Descrever os motivos que levam à escolha de iniciar ou recusar a PrEP oferecida a HSH e mulheres transexuais. 3) Descrever o número de soroconversões na coorte de participantes usando PrEP. 4) Descrever os padrões de resistência de medicamentos contra HIV entre pessoas que se tornem infectadas pelo HIV durante a participação no projeto demonstrativo de PrEP. 5) Avaliar o auto-relato de desvios (venda ou partilha) da PrEP. 6) Determinar as necessidades de espaço e equipe para administrar a PrEP no nosso meio. 7) Descrever os possíveis danos sociais decorrentes do uso de PrEP. 8) Descrever a prevalência de doenças sexualmente transmissíveis (sífilis, herpes simples-2, clamídia, gonorreia, hepatite B e hepatite C) na população do estudo.

Objetivo secundário:

- Acrescidos após a EMENDA: 9) Avaliar a adesão à PrEP através do monitoramento dos níveis sérios de tenofovir. 10) Avaliar viabilidade, aceitabilidade e efetividade de mensagens de texto (SMS) na população do estudo. 11) Avaliação da prevalência de sindemia (consumo de álcool e de drogas, violência entre parceiros de sexuais, depressão e

comportamento sexual compulsivo) na população do estudo. 12) Avaliação da aceitabilidade e conhecimento de métodos biomédicos de prevenção do HIV para adesão à PrEP na população do estudo.

Avaliação dos Riscos e Benefícios:

Permanecem os mesmos do Protocolo Versão 1.1, de 22/11/2012, aprovado em reunião de 26/11/2012 - Parecer 156.320, datado de 28/11/2012.

Comentários e Considerações sobre a Pesquisa:

Já foram considerados na primeira versão do projeto.

Considerações sobre os Termos de apresentação obrigatória:

Faz parte integrante deste protcolo: 1) TCLE versão 2.0 de 1 de novembro de 2013; 2) Bula do Truvada. Foram gerados a partir desta EMENDA.

Recomendações:

Não se aplica.

Conclusões ou Pendências e Lista de Inadequações:

Não se aplica.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

EMENDA apreciada e aprovada em reunião de 25 de novembro de 2013, tendo sido acatada pelo Colegido.

RIO DE JANEIRO, 26 de Novembro de 2013

Assinador por:
Léa Ferreira Camillo-Coura
(Coordenador)

Endereço: Avenida Brasil 4365
Bairro: Manguinhos **CEP:** 21.045-900
UF: RJ **Município:** RIO DE JANEIRO
Telefone: (21)3865-9585 **E-mail:** cep@ipec.fiocruz.br

ANEXO 3: E-mail de confirmação de aceite da publicação do primeiro artigo

Gmail Luana Marins <luanamarins.fiocruz@gmail.com>

Notification of Formal Acceptance for PONE-D-19-05684R2 - [EMID:0bc369740eb65c91]

1 mensagem

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PONE-D-19-05684R2
Performance of HIV pre-exposure prophylaxis indirect adherence measures among men who have sex with men and transgender women: Results from the PrEP Brasil Study

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