CONSULTATION ON PRE-EXPOSURE PROPHYLAXIS (PrEP) ADHERENCE

8 JUNE 2014
MIAMI, USA
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ACKNOWLEDGEMENTS

We would like to give a special thank you to Jessica Haberer for her assistance in organizing this meeting and for her excellent presentation which set the stage for a rich discussion. We would also like to thank Francois Venter and Jared Baeten who, along with Jessica Haberer, facilitated the different meeting sessions very effectively. Thanks are also due to all the meeting participants who contributed extensively to the debate and allowed for a successful outcome.

This meeting was organized by Kevin O’Reilly and Kathryn Curran with the support of Florence Koechlin. The report was prepared by Kathryn Curran and Florence Koechlin from the HIV Department of the World Health Organisation, with support from Kevin O’Reilly.

Generous funding was provided by the Bill and Melinda Gates Foundation.
EXECUTIVE SUMMARY

Adherence is a key issue in ensuring PrEP effectiveness. Adherence to study product varied widely across randomized control clinical trials, and clear evidence emerged from those trials that higher adherence is directly correlated to higher HIV prevention effectiveness. This meeting report summarizes the discussions and outputs of a consultation on how to measure PrEP adherence and equally how to interpret PrEP adherence measures beyond those clinical trials, in the context of demonstration projects and broader implementation.

PrEP demonstration projects are evaluating the safety and effectiveness of PrEP as part of a package of HIV prevention interventions for priority populations. Adherence will be at the center stage of these efforts. Conditions in demonstration projects may favor greater adherence, since there will be no equipoise, no placebo and since it will be offered to those who actually perceive a need for it, but it may also be lower due to less intense support. However, variability in adherence is expected in different settings. Finding the appropriate ways to measure and interpret it will therefore be critical to make sure the right guidance on how to support high adherence is developed for broader implementation and scale up.

The meeting stressed the following key messages

Real consensus was reached that adherence should be conceptualized differently for PrEP compared to ART. A new paradigm for measurement and interpretation is needed that includes factors such as user type, regimen, duration of use, and alternatives. Interpreting PrEP adherence by using the treatment model will likely result in underestimates of PrEP adherence that do not accurately reflect the degree of HIV prevention. Key differentiating attributes of treatment adherence versus PrEP were highlighted as follows:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PrEP</th>
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<tr>
<td><strong>Users</strong></td>
<td>Everyone living with HIV needs or will need treatment at some point</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>Treatment must be taken every day in a fixed schedule to be effective</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Once started, treatment must be taken for life</td>
</tr>
<tr>
<td><strong>Alternatives</strong></td>
<td>No alternative provides what treatment offers</td>
</tr>
</tbody>
</table>

It was proposed that a new terminology could also be helpful in stressing the difference between the two, using for example the terminology ‘Prevention effective adherence’. This term was suggested to capture the pattern of PrEP use that, while not reaching the standards for treatment adherence, would be sufficient to achieve meaningful HIV prevention.

It was also highlighted that there is no prefect way to measure adherence. A mix of measurement options was discussed: self-report (including SMS surveys), pharmacy refill data, electronic adherence monitoring (e.g., MEMS, Wisepill and other similar devices), drug levels (plasma, red blood cells, hair) are options to be considered. It will be necessary in each context to find a fair balance between (i) affordability, (ii) feasibility, (iii) compatibility with users’ lives, and (iv) triangulation of the strengths and weaknesses of the different adherence measurement methods selected to provide a sufficiently accurate picture of patterns of use. The importance of understanding patterns of use was emphasized over averaged estimates, which will not capture periods of low/no risk or use of alternate prevention methods.

The meeting participants also agreed that measurement is one part of the equation; the interpretation of the results then represents another important conundrum. One can use, for example, a mix of electronic adherence monitoring caps and self-report to understand when doses were likely taken, but the question remains how can those results be interpreted appropriately to get an accurate picture of adherence to PrEP? Additional
information about risk and other prevention behaviors is also needed. Using recommended treatment adherence (e.g., pills taken divided by pills prescribed) as the frame of reference would be inaccurate and possibly unhelpful.

It will be also critical to understand what was described as the ‘natural history’ of adherence to PrEP in a non-clinical setting. That is, how do individuals decide when and how to take PrEP and other HIV prevention tools? Analogies were made to women’s decisions for contraception and how those change with life circumstances and preferences. The only way to do so will be by measuring patterns of adherence in concordance with patterns of potential sexual exposure to HIV to get a true measure of ‘prevention-effective’ adherence.

A well-targeted set of messages for providers to use with potential and current PrEP users to encourage PrEP adherence and help with implementation was highlighted (see table 1, section 4).

Participants agreed on the following next steps: (i) One page summary of clear PrEP adherence messages for practical settings (ii) Development of practical guidance on measuring PrEP adherence to be developed with key partners and added to the Framework for country level protocol development. (iii) Conceptual guidance on how to interpret PrEP adherence data to be developed for publication in a key journal.
## ACRONYMS AND ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>antiretroviral</td>
</tr>
<tr>
<td>FT</td>
<td>emtricitabine</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>IAVI</td>
<td>International AIDS Vaccine Initiative</td>
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<tr>
<td>MEMS</td>
<td>medication event monitoring system</td>
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<tr>
<td>MSM</td>
<td>men who have sex with men</td>
</tr>
<tr>
<td>PrEP</td>
<td>pre-exposure prophylaxis</td>
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<tr>
<td>SMS</td>
<td>short message service</td>
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<tr>
<td>STI</td>
<td>sexually transmitted infection</td>
</tr>
<tr>
<td>TDF</td>
<td>tenofovir</td>
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<tr>
<td>TG</td>
<td>transgender</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. INTRODUCTION

PrEP is the use of antiretroviral drugs by HIV-uninfected persons to prevent the acquisition of HIV infection. Daily, oral PrEP is highly efficacious in preventing HIV acquisition when taken as prescribed. In July 2012, WHO recommended that oral PrEP be considered as a possible additional HIV intervention for HIV-uninfected individuals at high risk of infection (i.e. the HIV-uninfected partner of a serodiscordant couple; men and transgender women who have sex with men) and encouraged countries to undertake PrEP demonstration projects.

PrEP demonstration projects evaluate the safety and effectiveness of PrEP as HIV prevention for priority populations beyond the context of clinical trials. It should be noted that demonstration projects were the focus of this discussion, as opposed to clinical trials and open-label studies that follow those clinical trials, although a number of measures and approaches discussed would apply in those contexts as well. These demonstration projects offer PrEP as part of a package of HIV prevention interventions. They measure PrEP initiation/uptake, use and discontinuation, as well as use of other prevention methods, such as condom use, negotiated monogamy among seronegative couples, sexual abstinence and antiretroviral therapy (ART) initiation by HIV-infected partners. Therefore, it is critical to measure and consider PrEP use in a broader context of HIV risk and HIV prevention. For example, a woman may choose to use daily oral PrEP while she is in an HIV serodiscordant relationship and then discontinue when the relationship ends or after her partner has initiated ART and achieved viral suppression. Similarly a sex worker may choose to supplement his or her condom use with daily oral PrEP during periods of commercial activity, but may decide to cease PrEP use when taking an extended break from sex work. As an HIV prevention intervention, PrEP may be best suited for these uses during periods of high risk of HIV infection, not for a lifetime. In addition, though it is recommended for daily use, "nearly daily use" of oral PrEP may afford sufficient protection from HIV once levels of TDF-FTC have reached effective concentrations in target tissues (see section 3.2).

Though adherence is critical for PrEP efficacy, the success of PrEP as part of a complete package of HIV prevention interventions and for protection during periods of high HIV risk is more complex than daily use of a pill. Existing paradigms for measuring ART adherence may not apply to the use of antiretrovirals for prevention. Treatment adherence differs from PrEP adherence in the following key ways:

- Treatment, once started, must be taken for life. PrEP can be selected for periods of high risk and stopped at other times.
- Treatment requires high consistent rates of adherence to be effective (although newer regimens appear to afford similar benefits with lower adherence). PrEP (using tenofovir [TDF] or emtricitabine/tenofovir [FTC/TDF]) may still provide protection if taken less than daily, depending on overall adherence patterns and route and timing of exposure to HIV.
- People on treatment have no alternatives available that provide the treatment benefit. PrEP users may choose other means to prevent HIV acquisition, especially in periods when HIV risk is lower.
- People on treatment are under known, constant threat of viral replication- they have a known condition with known outcomes if non-adherent. PrEP protects against a possible exposure and possible infection- odds of exposure per event are not known and are often underappreciated.

For these reasons and others, current definitions and concepts of adherence based on the treatment adherence model may not be appropriate indicators for PrEP success.

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1 Four randomized controlled trials demonstrated that PrEP, when taken daily, is highly efficacious in preventing HIV acquisition (Baeten 2012, Choopanya 2013, Grant 2010, Thigpen 2012). Likewise, two randomized clinical trials of daily, oral PrEP found no efficacy for HIV prevention due to poor adherence (Marrazza 2013, Van Damme 2012).
3 PrEP use could be considered as successful when individuals take it nearly every day when using it as a primary HIV prevention tool.
2. **MEETING PURPOSE AND OBJECTIVES**

**Purpose**
WHO hosted a small consultation of key experts on the topic of PrEP adherence to discuss how to consider and measure PrEP adherence beyond the context of clinical trials. The primary focus of the meeting was the interpretation of adherence measures in the context of PrEP in demonstration projects and broader implementation.

**Objectives of the meeting**
The main objectives of this meeting were to:

- Discuss how to consider, measure, and interpret PrEP adherence, especially what information in addition to the standard adherence measures will be needed to allow for correct interpretation of the data on adherence
- Begin developing an outline for a framework to consider PrEP adherence and define when and how periodic use of PrEP may be effective for prevention of HIV
3. DEFINING PrEP ADHERENCE

ART / HIV TREATMENT ADHERENCE: STANDARDS AND COMPARISONS TO PrEP

The standards for successful ART adherence have changed with time and are often dependent on the treatment regimen and time on treatment. Now modern potent ART regimens (e.g., NNRTI or boosted PI-based regimens) allow for treatment success at lower levels of adherence (i.e., a greater degree of forgiveness). For example, if a person living with HIV is taking 80% of their antiretroviral medications, then he/she will have a high chance of viral suppression; prior standards dictated 95% adherence. Treatment success also depends on time – if a person living with HIV has been taking ARVs for long periods of time, even lower levels of ART adherence may be sufficient to maintain viral suppression. Patterns of adherence have also proved to be important. Treatment interruptions, when ARVs are not taken for 1 or 2 weeks perhaps because the person does not make it to the clinic, often lead to viral rebounds. Despite nuances that continue to emerge with newer regimens, the current ART adherence message still emphasizes that people on ART should maintain 95% adherence indefinitely. The expectation with treatment is that every person with HIV should be on ART and he/she should take antiretrovirals consistently for the rest of their lives.

ARV use is very different in the context of PrEP. Little is known about how people will use PrEP outside of clinical trials or what their patterns of adherence may be. As an HIV prevention intervention, PrEP may be best suited for use during periods of high risk of HIV infection, not for a lifetime. In addition, though it is recommended for daily use, “nearly daily use” of oral PrEP may afford sufficient protection from HIV once levels of TDF-FTC have reached effective concentrations in target tissues (see 3.2 below).

Moreover, the public health strategies differ between PrEP and ART. PrEP use is an individual choice, an opt-in strategy, while ART is increasingly becoming an opt-out strategy. Public health programs can also potentially offer PrEP as part of combination prevention to specific groups of people who may not be ideal users of other prevention methods and are at high risk of HIV (e.g., people in high incidence cohorts who have difficulty using condoms consistently).

3.1 PrEP Adherence measurement in demonstration projects and beyond

**Self-report measure options.** Different types of questions used to evaluate adherence may provide different levels of accuracy, as compared to objective adherence measures. Traditionally, self-report of adherence is measured through the number of missed or taken doses during a specified time frame (e.g. how many doses did you miss?), though these questions tend to produce high estimates of adherence that over-estimate adherence. Research suggests that questions that ask about rating of abilities to adhere and frequency of missed doses result in better correlations with electronically measured adherence with wider distributions of responses (i.e., individuals reporting non-perfect adherence). Novel self-report measures may include questions related to intention to use PrEP, concurrent use of alternate HIV prevention tools, and risk behaviors that determine need for PrEP use. In measuring intentional breaks, timing of these breaks and starting and stopping PrEP, one should be realistic in expectations of what PrEP users are able to remember and report (i.e., specific start and stop dates are unlikely to be recalled accurately at periodic study visits).

Self-reported data may be collected in person through questionnaire or ACASI. Also, SMS or text message survey collection of self-reported adherence can be a feasible and powerful, but imperfect, tool. SMS data collection will require consideration of missing data (e.g. unanswered text message surveys). For example, in the Partners Demonstration Project, a good response rate translated to about 75% of periodic, daily surveys answered (sent for the 14 days around each study visit). It should be noted that SMS or ecological sampling strategies may be best positioned within resourced projects. These provide nuanced adherence assessments over time which can be matched or combined with over time sexual behavior or injection drug use.

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6. Recommendations emerging from iterative cognitive testing to identify adherence questions that are consistently and clearly understood by patients on ART include (a) adopting a general recall approach (vs attempts at identifying specific doses missed); (b) favouring a “30-day recall” period (vs other time frames and phrasings such as “past month” or “past 4 weeks”); and (c) framing execution in terms of self-assessed performance (vs ability or percentages). Based on extensive research, Wilson and colleagues recommended the following phrasing: “In the last 30 days, how good a job did you do at taking your HIV medications in the way you were supposed to?” which is a revision to Lu and colleagues’ ability item.
behavior. Cost and potential Hawthorne effect or potential change in adherence behavior due to observation should be considered.

Self-reported data can be compared against objective measures (e.g., electronic adherence monitoring, see below) during demonstration projects to determine which approaches may be most informative in a given population. There does not seem to be one best way to ask about adherence.

**Pharmacy refill data.** Pharmacy refill data (e.g., whether or not a prescription was filled, picked up) provides an objective, but blunt measure of desired PrEP usage. It may be interpreted as maximal predicted PrEP adherence (i.e., the amount of drug available to a person, regardless of whether it was actually ingested). One should consider how well pharmacy refill data can assess adherence and whether it would be an adequate, single measure. Announced pill count was not recommended as an option, however it should be noted that medication possession ratio is not considered a bad measure.

**Electronic adherence monitoring.**

**MEMS.** MEMS offer an objective measure of adherence, allowing for analysis of daily patterns of pill use through recorded times of openings of medication bottles. The disadvantages of MEMS include the cost and potential Hawthorne effect (i.e., potential change in adherence behavior due to observation). One should consider how to understand and interpret times when the medication bottle is not opened. For example, does a lack of opening represent non-use or use of an alternate container? One should also consider whether MEMS can adequately assess intentional breaks in PrEP use. The LA PrEP demonstration Project includes a sub-sample of participants who have agreed to use a MEMS cap to better understand patterns of PrEP use. MEMS cap are being used to measure adherence during PrEP demonstration projects to learn how to measure and how to improve adherence, but they may not be feasible in program implementation.

**Wisepill and other real-time devices.** Real-time adherence monitoring devices function similarly to MEMS, but contain a SIM card for immediate data transfer over cellular networks. Real-time adherence data for ART use allows for providers to quickly identify treatment interruptions and respond. For open-label PrEP, real-time data is not needed, and may not be worth the cost and infrastructure requirements for measuring non-biological outcome, including the Wisepill device, mobile phones for users and internet access for receipt and processing of data. However, it may be useful in settings for which high levels of data loss are a concern or if populations are widely spread geographically.

**Drug levels (plasma, red blood cells, hair).** Drug levels offer an objective measure of use or non-use of PrEP. There is variability in the adherence interpretation from drug level data depending on timing of sample collection (e.g., what does a sample every 6 months tell you about behavior over that time frame?) and type of sample used (e.g. when to use hair or red blood cells vs. plasma?). Measurement of drug in hair or red blood cells samples may be more difficult and complex for labs to process. It is also expensive, costing between 50 to 200 USD per test. A French lab has developed a saliva test that can measure recent adherence (e.g. yes/no whether a recent dose was taken).

Different types of samples measure drug levels in distinct ways, providing different information about adherence and patterns. Samples with a short half-life of drug level measure recent pill use (e.g. Was a pill taken recently? Yes or no). Hair and red blood cell samples have a long half-life of drug levels of about 2-3 weeks. These measures can assess a steady state of drug in a person’s body from daily PrEP dosing over several weeks to months. These samples that measure a longer drug half-life allow for the calculation of average adherence over 1 to 3 months (e.g. a person has taken on average half of their doses in the past 1 to 3 months). The main caveat to this measurement is that it quantifies average adherence over a given time period and does not provide information about patterns in adherence (e.g. whether a person takes all doses at the end or beginning, of the month). 7

**Summary**

In PrEP demonstration studies, it is important to have a variety of measures of adherence to 1) obtain the best possible estimates of adherence (i.e., through triangulation) and 2) understand which tools work best in specific contexts and populations. This information will be important for guiding program delivery and practice. PrEP adherence measures should get to the important question of prevention-effective adherence, which relates to behavior and behavioral choices that define the necessity of PrEP specifically for HIV prevention. There is great utility in different adherence measures, but once adequate data on adherence and optimal adherence support have been obtained from demonstration projects, implementation

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7 Pill count: Jessica Haberer explained that she did not include pill counts in her presentation of PrEP adherence measures because announced pill counts usually do not perform better than self-report and therefore will not add beyond the measures presented above.
may proceed without such involved assessments, as has been the case with roll out of other prevention tools, like condoms and OCPs. The information is valuable, but must be balanced with the need for resources in other areas, such as community outreach and product itself. For example, programs that distribute condoms do not necessarily measure adoption, use, and adherence to condoms to evaluate and demonstrate program success.

Self-report may be useful in identifying individuals with challenges yet it cannot be the only measure in PrEP demonstration projects because it is an unreliable measure of adherence. Self-report may be reliable when a person says that they are not using a medication, so there is utility in asking someone about medication use. On the other hand, self-report may overestimate adherence when a person says he/she is using it. Demonstration projects can evaluate how self-reported adherence compares to other measures and quantify possible over-estimation. In addition, it should be noted that in the context of implementation, self-report is feasible and could be informative in identifying individuals with adherence challenges, especially if the self-report questions were tested in a given population during the demonstration stage.

**Additional discussion points:**

- **Who measures adherence?** The person or provider who poses/administers self-reported PrEP adherence questions to the PrEP user is important. It was discussed that it may be problematic for clinicians or care-team members to measure adherence in situations where there are real or perceived negative consequences to self-reporting non-adherence to PrEP. In such a situation, a clear separation between staff providing medication and staff measuring medication adherence may be needed. On the other hand, if a PrEP demonstration project offers PrEP as a choice of prevention and allows people to go on or off PrEP, then it may be preferred for a clinician to measure PrEP use and lead conversations with users about decisions to start, continue, and discontinue PrEP use.

- One of the participants noted that funders have spent over 250 million USD on PrEP studies and no more than 10 million USD on adherence measurement. It would be terrible to spend all this money with a public health intervention, knowing it works if people take it and yet not knowing why or how people took it. We do not want to repeat the same mistakes of the past, such as 1) not using objective behavioral measures (e.g. electronic adherence monitoring) in at least a subset of a study, and 2) not looking at adherence early in a study to see if the measures are working and adherence is adequate enough to warrant continuation or possibly indicate study design modification.

- Contraception and malaria prophylaxis offer a frame of reference. In South Africa, there are often administrative hurdles to getting a prescription for malaria prophylaxis. Also, one needs to be mindful that some adherence measures could limit people from actually using the drug (e.g., individuals may be dissuaded from using PrEP if they are uncomfortable with or do not have time for a required blood test to prove adherence prior to prescription renewal).

- Setting up PrEP delivery away from ART centers would provide an opportunity to use a ‘fresh’ and different approach to implementation and measurement of use and adherence than the one used for ART. Family planning clinics are one ideal point of PrEP delivery and integration, offering the opportunity to “marry” PrEP with contraception and “divorce” from ART. Another suggested option was to consider a pharmacy-based delivery.

- **Key research question: What is the natural history of adherence to PrEP in non-clinical trial settings?** Patterns of study product use have been examined; however, how PrEP will be used beyond clinical trials, particularly in relation to potential HIV exposures has not yet been established for any cohort. A number of possible scenarios of varying levels of concern for securing protection from HIV via PrEP were identified.

  - **Scenario 1- PrEP use followed by discontinuation.** If people take PrEP and then stop entirely, cleanly, then there is no benefit but there is no cost from medications nor toxicity. The only concern is whether these users reduced other prevention behaviors while on PrEP and fail to reinstate them post discontinuation. Emerging data suggests that starting PrEP and then discontinuing it may be a common scenario.

  - **Scenario 2- PrEP adherence corresponds to patterns of sexual exposure.** Here discontinuation would map onto potential HIV exposures. Concerns with securing PrEP protection here include accurate evaluation of HIV

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8 It should be noted however that a first review of key indicators conducted by the WHO did in fact not offer as much of a frame of reference as initially hoped when looking at contraception or malaria prophylaxis.

9 Grant RM et al. Results of the iPrEx open-label extension (iPrEx OLE) in men and transgender women who have sex with men: PrEP uptake, sexual practices, and HIV incidence. 20th International AIDS Conference, Melbourne, abstract TUAC0105LB, 2014.
exposure, re-starting with enough time to build high enough concentrations for PrEP to be effective, and continuing long enough after a potential exposure to prevention HIV acquisition.

- **Scenario 3**: limited PrEP protection due to inconsistent use. People who take PrEP intermittently (ongoing, but not daily), either every once in a while (or random use and non-use) but not reaching a minimum threshold (e.g., 4 pills per week consistently in MSM; the threshold for other populations has not yet been determined—see 3.2 below), are not expected to get benefit from PrEP.

- **Scenario 4**: Mis-matched PrEP use. The worst-case scenario is if people do not take PrEP when exposed to HIV, but take PrEP when not exposed.

The only way one will know how the natural history of PrEP adherence in non-clinical settings will play out is to measure patterns of adherence and patterns of sexual exposure. It is important to understand the behaviors in a setting similar to future program implementation.

### 3.2 New paradigm for PrEP adherence

While it is generally agreed that PrEP adherence is crucial, it is important to consider and understand what is PrEP adherence and what is PrEP non-adherence. PrEP adherence is important when PrEP is intended to prevent HIV. PrEP adherence is not important 1) when other highly effective prevention methods are being appropriately used and/or 2) when risk of HIV acquisition is not present (e.g., no sex).

Therefore, **data are needed on use of all HIV prevention methods (e.g., condoms, HIV-infected partner use of ART) as well as HIV risk**. Consideration should be given to the efforts invested in understanding adherence to each HIV prevention method and the validity of data on HIV risk.

Participants discussed the concept of **coverage**—whether a PrEP user was “covered” at the time of the HIV exposure at a level to protect against infection. This measure could be determined by assessing possible exposures (e.g., sex, sex without a condom) and the drug concentration during the same time period. The Partners Demonstration Project adherence sub-study is using daily, automated SMS surveys in a sample of participants to measure self-reported HIV risk behavior and PrEP adherence over a 14-day period (one week before and one week after quarterly clinic visits). These data can be compared to drug levels measured at quarterly clinic visits to try to answer this question.

**Defining periodic versus intermittent PrEP**

- **Periodic PrEP** or “seasons of PrEP” may entail the use of PrEP during certain timeframes of HIV risk with defined starts and stops.

- **Intermittent PrEP** may refer to an official prescription of intermittent non-daily PrEP use, as was examined in the IAVI study\(^\text{10}\) and is being examined in the IPERGAY\(^\text{11}\) trial and HPTN067\(^\text{12}\) for feasibility of diverse dosing strategies. It may also be “unofficial” or reflective of how many people actually take PrEP daily as prescribed (e.g. not 100% daily use of PrEP).

- **Intermittent but consistent PrEP**: Are 4 doses of PrEP per week on average enough for protection? Peter Anderson and colleagues published an analysis of iPrEx trial data that estimated 96% efficacy of TDF in preventing HIV with 4 doses per week.\(^\text{13}\) Women may need more doses to get the same level of protection as men. Peter Anderson explained that the issue is that tenofovir accumulates in rectal tissue more quickly and in higher levels compared to vaginal tissue. For MSM, 4 doses per week on average is an adherence level that achieves the EC90 (the concentration of drug that achieves 90% of maximal effect). This may not translate to women or men in heterosexual relationships.

Long half-life measures (red blood cells, hair) provide thresholds of levels that are associated with an adherence rate. One will get information from PrEP demonstration projects to better understand the natural history of adherence. What role do these measures have in the context of prevention effective adherence? Will summary data be informative or are patterns required? One of the participants argued the need for electronic adherence data to understand drug levels, and provide evidence that 4 doses per week (shown through bottle openings) achieved a certain drug level or range (again, possibly appropriate for MSM, not clear for other populations – see section 3.2).

Peter Anderson described their ongoing directly observed therapy study in Colorado, in which they are collecting red blood cells (every 2 weeks) and hair (every 4 weeks) samples to measure drug concentrations with different dosing patterns over 3 months, drug holidays and intermittent use.

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11. CTN 268 ANRS program – IPERGAY trial - On demand antiretroviral treatment as pre-exposure prophylaxis for HIV infection in men who have sex with men in France and Canada.


This study will estimate threshold of drug concentration for efficacy and numbers to associate with adherence rates. Results are expected in a year and half (end 2015).

One of the participants commented that results from HPTN 067 ADAPT study would be available in a year (mid 2015) and reveal adherence patterns using Wisepill and three different dosing regimens, including intermittent PrEP.

3.3 Interpretation of PrEP in the context of other prevention methods & periods of risk

Two key concepts were discussed: execution of adherence and persistence of adherence. Execution of adherence describes how well an individual takes or adheres to PrEP during a defined timeframe of intended use (i.e. weeks or months when PrEP is the primary HIV prevention method). Persistence of adherence is the length of time than an individual takes PrEP.

Participants discussed how in other health fields, in particular reproductive health and contraception, the philosophy of adherence measurement in programs is very different (although not necessarily correct). Reproductive health programs rarely measure adherence and reasons for stopping or taking breaks. Most studies instead examine persistence (typically through pharmacy refills) and look at coverage through at least one method. Also, it was noted that 12-month pharmacy refill for contraceptives is often incredibly low.

How do we ask about intentional PrEP use or non-use?

In the Partners Demonstration Project, interviewers ask questions such as: Since the last study visit, was there any period of time when you deliberately decided to take a break from taking PrEP? Why? How many deliberate breaks were there since the last attended study visit? How long was your longest break? During the longest break, why did you stop taking PrEP? What other prevention methods did you use during PrEP use and breaks? Did you start taking PrEP again after this break? Performance of these questions is under analysis.

It may be difficult to obtain exact, accurate dates of PrEP start or stop, but there may be more reliable ways to record breaks from PrEP use, including the presence, duration of break, and context of break (e.g. not using PrEP because not having sex, or a consistent condom user).

The Partners Demonstration Project is assessing PrEP breaks through self-report and MEMS. Jessica Haberer reported preliminary findings stating that about 10% of PrEP users report ever taking a break. Then, comparisons of self-report can be made to the MEMS data. There may be periods where a person stops PrEP use, but does not perceive it as a break. A counseling message may state, “If you stop taking PrEP, it is okay, just let us know and come back in to re-test before you start again. Let’s also talk about your needs and determine if potential other HIV prevention tools may make sense for you.”

How do we define PrEP adherence in the context of actual risk (instead of perceived risk)?

In the context of contraception for pregnancy prevention, providers present a suite of options and methods and ask the woman which method they prefer to use at the time. Likewise, at an HIV clinic, a provider may discuss risk, present a range of HIV prevention options to an HIV negative person and ask: Which HIV prevention method are you going to use (e.g. not having sex, know partners status, partner on ART, condoms, PrEP)? The goal is to determine if and how the individual is achieving highly-effective prevention.

PrEP adherence is important in the context of actual risk of HIV transmission. PrEP use is not relevant if there is no risk of HIV transmission and no HIV risk behavior.

A few proposed measures

Percent adherent to PrEP: Number of persons prescribed PrEP who are taking PrEP during a specific time period out of all prescribed PrEP users, by defined population and time period

HIV prevention coverage: How many times did you have sex in a 30-day period? On how many of those days did you take PrEP? What other prevention tools did you use, if any, and when? This question will help with risk and true coverage (e.g. 100% condom use would equal 100% coverage even if PrEP was spotty)

Deciding to take PrEP: How well did they take PrEP when they decided to take it?

Important to the coverage measure, it was noted that a person would probably need a week of dosing before an event of potential HIV exposure and probably a week of dosing after the event for high-efficacy prevention coverage solely through PrEP. Unless IPERGAY shows that event-driven PrEP dosing works, PrEP users will be taking PrEP for a certain period of time, not just as needed.

14 Haberer J et al. Adherence to Pre-Exposure Prophylaxis (PrEP) in the Partners Demonstration Project: Preliminary Findings. 9th International Conference on HIV Treatment and Prevention Adherence, Miami, FL, USA. Oral abstract #317.
4. PrEP ADHERENCE IN PRACTICAL SETTINGS

Models of delivery of PrEP will differ by setting. For example, three settings may serve as examples that are useful to consider: 1) US: high income, guidance available, already being prescribed, 2) South Africa: middle income, not dependent on donor funding, but skeptical of whether PrEP is a priority; and 3) Uganda: not independent from donor funding, people not in a position to pay for PrEP.

PrEP adherence is successful when people are taking it, taking it well enough, and when there is exposure. What is enough?

Mathematical models and subgroup analysis from PrEP clinical trials suggest that very high levels of adherence lead to very high levels of efficacy. Also, there is some level of forgiveness if a dose(s) is missed. It is still unclear what enough really is for different populations at this point. One study suggests 80% during periods of risk, based on the partners PrEP Ancillary Adherence Study data. In this context, the need to collect data to determine when there are periods of risk is particularly important.

What is the message on condom use and dual protection?

Are people being told that they need to use both? The efficacy data from clinical trials was based on promotion of concurrent condom use; however, many individuals may be looking for alternatives to condom use.

At the Thika site of the Partners Demonstration Project, staff always tells people to use condoms and PrEP, but they do not tell them to make a choice between HIV prevention methods. They do not tell them to use PrEP instead of condoms. There is an understanding that even couples who choose to use condoms may experience need or desire for another HIV prevention option. Sometimes they may want or need a condom break. There are also people who are inconsistent condom users or non-condom users and often one cannot predict when there is a time that one may not be able to use condoms (for example if drinking alcohol, one may not anticipate sex). Note was made that quarterly clinic visits and counseling often lead to increased perception of HIV risk as well as increased condom use.

It was noted that someone who is struggling to use condoms or not willing to use condoms is a good candidate for PrEP. Also, in other health fields, providers do not tell people who are at risk of heart disease to choose one prevention method (e.g. if you take a statin, you don’t have to exercise at all). For PrEP, providers can counsel about partner reduction, partner choice, testing partners, condoms, etc. They may also tell them that they will have more control over whether they take PrEP themselves than over their partner taking ART. PrEP is one of many things one can do to prevent HIV.

It should also be highlighted that if there is an elapsed time when PrEP has not been taken in a certain number of days, then condoms should definitely be used.
Box 1: Messages for PrEP adherence and implementation

PrEP adherence:
- It works if you take it. Do you want it?
  - It is highly effective if taken every day
  - Optimal protection from HIV and other STIs, as well as pregnancy, can be achieved with concurrent condom use
  - Take it every day (one pill per day)
  - There is forgiveness if you miss an occasional pill
  - Routine (taking at the same time) is important for remembering to take it everyday. If you forget, take your pill as soon as you realize it
  - There are occasional side effects (especially the first month)
  - Alcohol or lack of food will not interfere with PrEP use
- Before: Take one pill a day for one week (before exposure)
- After: Take one pill a day for one month (after last exposure)
  - No data, but 28 days is the recommendation for post-exposure prophylaxis
- If you are unable to take PrEP on a daily basis, use other HIV prevention methods during that time
- Talk to your partner and family about having tablets. Address the potential of false disclosure (assumption taking ARVs indicates being HIV positive and taking HIV treatment)

PrEP adherence support
- What is your plan for remembering to take a pill every day?
- What are your facilitators and barriers to consistent pill use?
- Daily routines and habits can be good reminders for pill taking
- Engage your partner for adherence support if you can
- Make a plan for how to deal with false disclosure if you are seen taking PrEP

Routine assessment of PrEP adherence
- Are you still taking PrEP to protect you from HIV?
- Have you taken a break from taking PrEP / stopped taking PrEP?
  - Why did you stop?
  - Were you protected during the time you stopped taking PrEP?
- Side effect assessment
  - Have you had any problems?
  - How have side effects affected your adherence?
  - Is there anything you can do to make the situation better?
- Intensive adherence measurements are not advocated in routine practice
- If poor adherence: Do you still want it? If yes, identify and address barriers to adherence. If no, suggest other HIV prevention methods
Prevention-effective adherence – a new adherence term for PrEP. For PrEP, prevention-effective adherence is needed. Prevention-effective adherence entails taking PrEP when there is a potential exposure to HIV and taking enough PrEP to achieve HIV protection (between 4 to 7 doses per week; it may depend on population and results of ongoing trials - see section 3.2).

Programmatic success of PrEP is increased coverage of HIV prevention and filling the prevention gap. Prevention-effective adherence also translates to other future HIV prevention intervention options, including injectable PrEP and microbicides.

Populations who may benefit the most from PrEP may be those who are not using condoms. A secondary analysis of iPrEx trial data suggests that PrEP could be highly effective at preventing new infections among MSM and TG women. A very high impact was seen when the analysis was limited to a subgroup of MSM and TG women that report high-risk behavior (i.e. receptive anal intercourse without a condom in the past three months). The overall number needed to take PrEP to prevent one new HIV infection per year was 62 for the entire study cohort, and as low as 36 for the subgroup of MSM and TG women reporting receptive anal sex without a condom.16

Programmatic effect. The following approach was discussed during the meeting, but full consensus was not reached on its appropriateness. There are enough people coming to the program and doing well enough that there is a programmatic effect. It is not 100% of “at risk” people or 100% adherence for people taking it. The contraception field offers a useful analogy. Family planning programs do not measure pregnancy outcomes or periods of risk (for pregnancy), but they know how many people come to the clinic/health center and how many people take contraception. Oral contraceptives are often dispensed to prevent pregnancy without measuring adherence or pregnancy outcomes. The success of the program is therefore evaluated on the number of people who come to the clinic.

Working with PrEP users in a programmatic setting (see also Text Box 1)

When and how should adherence be monitored? How should starting and stopping patterns be monitored? Persistence?

It may be most important to monitor PrEP adherence close to the time of initiation, although adherence behavior, preferences, barriers and facilitators can change over time (as observed in Partners PrEP17 and iPrEx OLE,18 participants switched between high and low adherence per drug level testing).

Again, it should be noted that self-report is unreliable. Demonstration projects would be an ideal setting for testing self-report questions that may reveal adherence challenges. Ongoing counseling and check-ins will be very important. Counseling could follow the contraceptive lead and be geared toward whether PrEP is the right choice now. For instance, “How is PrEP working for you as your primary HIV prevention tool?” That would be a way to open up the conversation to adherence. Ira Wilson and colleagues suggest asking medication users: “How well have you adhered?” If a person reports less than 100% adherence then it opens the door to counseling and identifying interventions to overcome challenges (it should be noted however that we don’t know yet how this performs in practice). For users who report intentional non-adherence or taking a break, the counseling message should be about other HIV prevention options. In the Partners Demonstration Project, 10% of PrEP users reported taking breaks; 25% of breaks were due to perceived side effects, while 15% were for reports of feeling unwell. For PrEP, counseling may also address false attribution of side effects to PrEP.

For users who are struggling to take PrEP and want to continue with it, there is a need for adherence counseling. The provider can assess whether the person wants to be on PrEP and if not, suggest another method that fits the person’s lifestyle. If the person does want to continue taking PrEP, then the person may need additional counseling and support to identify and overcome barriers to adherence.

In the first month of PrEP use, adherence counseling and provider messages should focus on potential start-up side effects. Providers can talk to users about how to

develop a habit and have the user come up with a method for remembering how to take it and potential adherence challenges (e.g. What will you do when you have trouble taking it? How will you get support?).

Providers may also convey a message that there is still HIV prevention efficacy with missed doses and advise use of additional HIV prevention methods. The message around condom use is difficult. PrEP may be effective without condoms and may be an attractive alternative to condoms for those who do not wish to use them or cannot negotiate their use; however, clinical trial efficacy data was based on concurrent condom use recommendations and condoms have other purposes. A provider may explain, "PrEP will reduce your risk for HIV, but not other STIs. Condoms will reduce HIV risk even more and can also prevent pregnancy (if appropriate to the individual)."

Criteria for recruitment, adherence, and retention for PrEP demonstration projects?
It was mentioned that the Gates Foundation has defined three criteria for "go or no go" that may determine the continuation or halting of current funding for seven PrEP demonstration projects: 1) recruitment, 2) adherence, and 3) retention. Participants discussed that there will be enormous learning about the natural history, distribution, and patterns in PrEP adherence behavior in these settings, which are different than clinical trials. Thus, all adherence and retention data collected are informative. Also, these demonstration projects are different from clinical trials, in which a certain number of people were needed for enrollment and follow-up for statistical power to answer a scientific question.

The inability to start a demonstration project and/or recruit participants are fair criteria, but the context is really important, such as delays due to regulatory approval process. Based on their experience with the Partner PrEP Study and the Partners Demonstration project, a few consultants noted that recruitment during the first period is always slower than anticipated. It will be critical to understand why the study does not start or recruit as planned. A suggested minimum acceptable target may be 20% of recruitment planned for year one. Participants also discussed how in some settings, such as West Africa and India, the demonstration projects aim to deliver PrEP in a setting where nothing like it has been done before. Therefore, there will be a lot of programmatic work to do to get it started.

Corrective action plans are another option. If a study does not meet a certain percentage of their recruitment target, they will need to implement new recruitment strategies. The studies should also include other outcomes and methods to better understand why adherence is poor, if it is poor. Finally, it will be important to consider that the majority of the data in early assessments of PrEP demonstration are early patient data. The most difficult part of adherence is typically during the start-up or initiation of a new medication.

Use of biological markers to measure adherence?
Programs can implement PrEP without biological markers for adherence. The measurement of biological markers of adherence should not be a prerequisite of PrEP implementation. It was essential in clinical trials, and is important in PrEP demonstration projects to motivate governments and funding for future PrEP programs as a marker of success (and to compare to other adherence measures). If demonstration projects show they are incredibly useful, then it may be considered for program implementation and scale-up. Research could be directed to the development of feasible testing strategies (e.g., inexpensive point-of-care testing). Programs do not want to pose barriers to returning to clinic, and providers want to be able to offer different prevention strategies if PrEP is not working.

It was noted that if there was a drug level associated with efficacy, then biomarkers could be useful in assessing whether a user has effective concentrations. For example, a long half-life adherence measurement provides information on cumulative dosing, and could potentially be informative for a clinician to know whether there is enough PrEP in the system to be protective. However, patterns of risk and PrEP use should be addressed, as they will not be assessed through a summary drug level.

Compared to other health fields, which health programs use biological marker?
In the US, HIV RNA (or viral load) is used to measure ART adherence and treatment success, but in Kenya, Uganda, and other settings, this test is not routinely available. Undetectable HIV RNA suggests adequate adherence, while a detectable level can indicate poor adherence and/or the possibility of drug resistance. Family planning programs are implemented without any biological markers. Diabetes management uses biomarkers for guiding therapy, but psychiatry does not with most drugs (although it does with lithium). Do the new US statin guidelines require measuring lipid levels still? This could be another good analogy for PrEP.

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The following three activities were suggested to continue moving the adherence conundrum forward:

1. **One page summary of clear PrEP adherence messages for practical settings**
   Using key points from text box above, may be modeled after a one-page flowchart of instructions for contraception use in Kenya and other projects.

2. **Development of practical guidance on measuring PrEP adherence**
   To be developed by WHO with key partners and added to the Framework for country level protocol development.

3. **Communicating products of this discussion via an opinion paper (Jessica Haberer to lead)**
   Objective: Define success for PrEP adherence & a new paradigm. Introduce concept of prevention-effective adherence. This is not the treatment adherence paradigm. Many other things we do in health that are more analogous to PrEP than treatment, such as contraception. We need to marry PrEP to reproductive health, move it away from treatment (especially for women; for men, STI treatment clinics may be a better starting point.

Paper outline:

I. **Introduction**

II. **Measuring PrEP adherence**
   a. Clinical trial measures, goals, what we learned and issues
   b. Demonstration project (closer to implementation in real life) measures, goals, what we learned and issues
   c. Implementation measures and issues
   d. Clinical trials inform demonstration projects, but cannot assume adherence will be the same in both. Practice will be informed by demonstration projects.
   e. Need for better understanding of the natural history of PrEP adherence behavior

III. **Differences**

IV. **Prevention-effective adherence**
   a. Adherence during period of HIV risk
   b. Failure to adhere vs. transition to other prevention methods

V. **Adherence and efficacy relationship, behavior**

VI. **Defining periodic and intermittent PrEP adherence**

VII. **Breaks, forgiveness**

VIII. **Similarity & differences with ART and contraception**
   a. Julie Myers et al. piece in CID compared PrEP to OCP, but did not talk about adherence.

IX. **Learning from other prevention medications (statins, etc) & other analogies in health**
   a. Diabetes
   b. Prevention of myocardial disease – would never recommend just use one prevention strategy (David Glidden’s chart with statins, NNT)
   c. Malaria
   d. TB
   e. Tobacco control

X. **PrEP pathway**

XI. **Messages for implementation (e.g. Text box 1)**

XII. **Defining programmatic success (PrEP adherence)**

**Figure to illustrate prevention-effective adherence?**

**Table or graphic 1: Similarities and differences between PrEP adherence, ART adherence and contraceptive adherence**
- Outcomes, goals, patterns, challenges
- Similarity: have to take to have any benefit
- ART adherence success is relatively easy to measure because there is surrogate measurement viral that is close to behavior, while for PrEP this is more difficult (dichotomous, rare outcome of seroconversion)
- Similar to ART and contraceptive there is some forgiveness, do not want to take away if not 100% adherent. PrEP is likely more forgiving than ART and contraceptive when missed doses.

**Graphic: 2 - PrEP pathway**
- The PrEP pathway (prevention continuum, phases of PrEP use?) is not a cascade, it is different than treatment cascade
- Treatment cascade, each step is a loss, whereas for PrEP, you can fill in the gaps
- Access decisions – starting, continuing, stopping, it is not a public health failure
- There are lateral changes in the PrEP cascade that make it less of a waterfall
- Initiation, implementation, interruption
- Access, decision, start, continue, stop, side arrows (condoms, ART, behavior change not necessitating PrEP)
# AGENDA

**WHO Consultation on PrEP adherence**  
Loews Miami Beach Hotel, Miami, Florida, USA

**SUNDAY, 8 JUNE 2014**

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<tr>
<th>Time</th>
<th>Agenda Item</th>
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<tr>
<td><strong>08:30-09:00</strong></td>
<td><strong>Welcome &amp; Introductions</strong></td>
<td>Kevin O’Reilly</td>
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<td></td>
<td>– Overview of meeting agenda, objectives and outcomes</td>
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<td>– WHO guidance on PrEP and need for implementation guidance</td>
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<td><strong>SESSION 1</strong></td>
<td><strong>GROUP DISCUSSION OF PrEP ADHERENCE</strong></td>
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<td>09:00 – 11:00</td>
<td><strong>How do we define adherence to PrEP?</strong></td>
<td>Jessica Haberer</td>
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<td>– Measurements in clinical trials and demonstration projects</td>
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<td>– New paradigm for PrEP adherence</td>
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<td>• Understanding when adherence is and is not important</td>
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<td>• Defining periodic versus intermittent PrEP</td>
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<td>– Interpretation of PrEP in the context of other prevention methods</td>
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<td>&amp; periods of risk</td>
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<td>11:00 – 11:15</td>
<td><strong>Break</strong></td>
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<td>11:15 – 12:30</td>
<td><strong>PrEP adherence in practical settings</strong></td>
<td>Francois Venter</td>
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<td>– Periodic PrEP in practice (associated counseling messages)</td>
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<td>– PK modeling in different populations and implications for guideline</td>
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<td>development (e.g., intermittent PrEP use)</td>
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<td>– Messages for health providers and PrEP users</td>
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<td>– Adherence feasibility assessments in different populations (not taking</td>
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<td>on too much); pairing with interventions</td>
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<td>12:30 – 13:30</td>
<td><strong>Working Lunch</strong></td>
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<td><strong>SESSION 2</strong></td>
<td><strong>DEVELOPMENT OF OUTLINE FRAMEWORK FOR PrEP ADHERENCE</strong></td>
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<td>12:30 – 15:30</td>
<td><strong>Framework to consider PrEP adherence</strong></td>
<td>Jared Baeten</td>
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<td>– PrEP adherence measurement in real world</td>
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<td><strong>Suggestions for way forward</strong></td>
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### LIST OF PARTICIPANTS

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