PrEP demonstration projects:

A framework for country level protocol development

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EXECUTIVE SUMMARY – KEY ISSUES

1. **Creating and sustaining adherence** (see page 19, 22, 25)
   Daily oral PrEP clinical trials to date have shown that adherence is the one single factor that influences most PrEP effectiveness. High levels of drugs found in the participants' blood had a direct correlation with high levels of protection. On the other hand, ensuring those high levels of adherence has proved a very serious challenge in some contexts. Finding ways to ensure that high (if not perfect) levels of adherence are met should therefore the first area of focus.

2. **Measuring adherence** (see page 11, 20)
   Numerous methods for measuring adherence are available, with different costs, difficulties and reliability. A variety of approaches are presented. Placing adherence to PrEP in the context of combination prevention will be intellectually challenging but is essential for

3. **Measuring impact and modelling incidence** (see page 14)
   Comparing observed HIV incidence to that of comparison populations either observed or modelled.

4. **Secondary endpoints** (see page 15)
   Sexual behaviour, pregnancy, drug resistance, STIs, selected factors from users' perspectives.

5. **Primary study populations** (see page 10, 16)
   The choice of populations to be covered in a PrEP demonstration project should be context dependent, based on the greatest need within the country/region where the demonstration project is to take place. These may include may include sero-discordant couples in generalized epidemics, men who have sex with men and sex workers in concentrated epidemics, and other high-need groups (such as mobile populations, truckers, etc.) in concentrated epidemics. In addition, geographies of needs/risks may be considered.

6. **Study design and sample size, length of project** (see page 16, 24)
   The precise study design, sample size and length of project should be defined based on the specific setting and population where the project is to take place. A rough estimate of 600 to 800 individuals for each demonstration project group, and of at least 12 and if possible 24 months for the duration of the project should be considered as a minimum. A number of parameters that may need to be considered in refining these parameters are listed in this document.

7. **Daily dosing, periodic dosing and intermittent dosing** (see page 19, 21)
   Placing PrEP in the context of combination prevention reflects more accurately the realities of people's lives but complicates the administration and the measurement of the intervention. PrEP works best when taken daily. The aim should be to be as close as possible to this target. Intentional intermittent dosing is not endorsed.

8. **HIV testing, retesting and drug resistance** (see page 13, 15, 18)
   Ensuring that an individual does not start PrEP if HIV positive or discontinues immediately when seroconverting is critical both for the person's own safety and for the population at large, to avoid the risk of developing drug resistance. At this point however, as long as the specific recommendations detailed in this document are followed, it appears that resistance may not pose too serious a threat in regards to PrEP. Indeed, this is a drug used in uninfected people. Specific recommendations on initial testing protocol and retesting can be in the document.

9. **Other safety issues (side effects, pregnancy and breastfeeding)** (see page 20)
   The monitoring of side effects and other potential safety issues is a critical component of a PrEP demonstration project.

10. **Sustainability** (see page 27)
    The most useful evidence drawn from these demonstration projects will be grounded in the reality of existing health systems, and therefore working jointly with the health system from the early stages will be beneficial for eventual uptake of PrEP on a larger scale. For that purpose, the demonstration projects should include three additional steps (i) identifying the functions / services that the health system would need to implement the components of a wider program, (ii) carrying out an assessment about the readiness of the health system/sector to carry out PrEP, (iii) carrying out a costing exercise for the program as a whole and for individual program components.

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ACKNOWLEDGEMENTS

This document is the result of the efforts of many people whom we would like to thanks. A first draft was prepared and shared for a round of comments prior to a meeting held in July 2012 in Washington. During the meeting, the key components of this document were discussed and reviewed in detail by the participants: Jared Baeten, Carlos Caceres, Connie Celum, Amy Cornelli, Ide Cremin, Lut Van Damme, Vincent Douris, Mark Dybul, Robyn Eakle, Emily Evens, Peter Fajans, Tim Farley, Bob Grant, Jessica Haberer, Tim Hallett, Cate Hankins, Caitlin Kennedy, Susan Kim, Heidi Larson, Tim Mastro, Veronica Noseda, Peter Piot, Dawn Smith, Michael Sweat, Betsy Tolley, Mitchell Warren, Brazey de Zalduondo. The document then underwent a number of iterations as more information became available and as more comments were provided by the participants. It should be noted that this is a 'living document' therefore later versions will be made available as the thinking on the topic advances.

The meeting and document were organised and produced by Kevin O'Reilly and Florence Koechlin McGillivray of the HIV Department of the World Health Organization, with the support of Varja Lipovsek, a consultant to WHO, and Susan Kim of the O'Neill Institute, Georgetown University Law School.

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PREFACE

Why is this document being written?

Countries considering undertaking PrEP demonstration project research face many challenges and decisions, and this document is an attempt to clarify and if possible simplify them. The document is not meant to be proscriptive. If countries identify a nationally or locally relevant issue not covered here, they are encouraged to include it in their PrEP research. This document is meant to be a 'living document'. As the thinking and knowledge progresses, and as new specific tools are developed for use in these demonstration projects, new updates will be produced.

The demonstration projects are aimed to serve two purposes: 1) enable countries to learn enough about implementation issues related to PrEP so that the transition between research, including demonstration project research, and the wider expansion and institutionalization that is entailed in scaling up implementation is more feasible; and 2) enable WHO to extract generalizable information for the eventual development of guidelines for PrEP delivery more generally.

What should be the main outcomes studied?

It is becoming clear that PrEP is effective in preventing HIV acquisition if it is taken as directed or nearly as directed. It is also clear that PrEP may be an expensive way to prevent HIV. For a country wishing to implement an effective PrEP intervention, two key challenges must be met: showing that PrEP can be delivered safely in a way that promotes and supports high medication adherence and showing that PrEP can have an impact on HIV transmission. It is recommended herein that one of the primary outcomes of interest is adherence to the PrEP regimen, as studies have clearly shown that adherence is the largest determinant of effectiveness of PrEP. The second outcome to be studied is impact. A true impact study is an entirely different undertaking from a demonstration project, however, and is beyond the scope of what is described in this framework. However, with frequent retesting and good adherence data, it should be possible to compare incidence in the PrEP-using group to the known incidence in similar people not using PrEP. When incidence is not known for that group, it should be possible to use mathematical modelling to estimate an incidence figure for comparison purposes to estimate impact. However, one should remember that this modelled impact will be a rough measure at best and will likely have very wide confidence intervals.

The studies anticipated will have smaller sample sizes than the efficacy trials of oral PrEP. For this reason, the ability to pool data from demonstration projects and from follow-on studies to the clinical trials may be important. Reasonable comparability of protocols, at least on some key measures, will be helpful in this regard.

Who will benefit from the outcome of this research?

It is our hope that countries will find the process of designing their research facilitated by using this document, and that they will be better able to generate the necessary proposals for obtaining funding for the planned research. It is also our hope that the use of this framework will foster cross-country comparisons of results and will ultimately result in the types of implementation data that WHO will need for the development of guidelines.

Why are we calling this "demonstration project" research? What questions are we trying to answer?

Demonstration projects are an intermediary step between initial efficacy research and full-scale implementation. They "demonstrate" that something which proved to be effective in a controlled trial can actually be implemented in settings reflective of real life and real health system challenges. As such, they are an important step when the intervention in question may have significant challenges to its implementation. If we take the completed trials on PrEP effectiveness as the research evidence base, then the key question is how best to implement PrEP safely and effectively in specific country contexts. The recently issued Guidance on PrEP recommends demonstration project research to identify the best ways to deliver PrEP safely and effectively, to achieve the highest level of adherence possible. The central point is that countries, by undertaking this research, are planning for the eventual introduction and scale up of PrEP, assuming the results are positive.

Is it oral PrEP, topical PrEP or both?

This document is addressing only oral PrEP, as that is the product that is already available and licensed for distribution and use. However, as many of the questions to be explored are also relevant for topical PrEP (antiretroviral microbicides), we hope that lessons learned in this effort will be useful for topical PrEP as well. In addition, we hope protocols that arise from the use of this framework can also address the use of PrEP in the context of greater emphasis on "treatment as prevention" or early treatment with antiretroviral therapy for HIV-infected individuals (Cohen et al, 2011). PrEP should ideally not be delivered as a stand-alone program as it gets rolled out. Finally, the framework does not exclude the possibility that lessons will be learned which will be equally valuable for the next generation of PrEP products.

Is this for generalized epidemics only?

From the outset, it has been hoped that PrEP would be a powerful tool against HIV in the most profoundly affected generalized epidemics and could be used strategically to alter the course of the epidemic in those settings. Research on PrEP effectiveness has largely focused on generalized epidemics, but has specifically focused on selected higher risk people in the generalized epidemic context: Partners PrEP in heterosexual serodiscordant couples, TDF2 in high risk heterosexual men and women, and FemPrEP and VOICE in high risk women. Importantly, effectiveness research has also been conducted in concentrated epidemics: iPrEx in men who have sex with men. We have tried to develop this document to allow its use in developing protocols for both targeted populations in concentrated epidemics as well as in generalized epidemics.

Will the document facilitate development of studies that are generalizable?

The studies to be fielded in countries will likely be small in size (compared to the effectiveness trials) and tailored to specific national and sub-national implementation settings and challenges. Nonetheless, we hope that studies developed under this broad framework will have enough similarities and will use sufficiently similar indicators and measures to allow cross-site and cross-country comparisons on key implementation questions.

I. BACKGROUND & RATIONALE

New approaches for preventing HIV infections are still needed, as more than 7,000 people continue to become infected around the world every day (approximately 2.7 million per year; UNAIDS 2011). The United States Food and Drug Administration (FDA) has, in mid-2012, approved TDF/FTC oral pills for use in HIV prevention. This decision was based on results from recent clinical trials testing oral (pills) PrEP among men who have sex with men (Grant et al 2010), and among sero-discordant couples (Baeten 2012), which proved that these drugs can substantially reduce the risk of acquiring HIV and was further supported by the results of the TDF2 study in Botswana (Thigpen 2012). In addition, PrEP has the potential to address the need for a female-initiated prevention method for women worldwide who may be, for a variety of reasons, unable to negotiate condom use, or who may find themselves in situations in which condoms are not available or their use is not feasible or desired.

This protocol framework proposal focuses on oral PrEP (TDF/FTC pills), the product tested in the clinical trials cited above. Oral PrEP may also be achieved through the use of tenofovir alone, though the effectiveness data are more limited and the observed effectiveness is somewhat lower than that of the TDF/FTC combination. In addition, a tenofovir PrEP vaginal gel product has also been subject to clinical trials but evidence has not been as conclusive – i.e., while shown to be effective in CAPRISA 004 trial (Karim 2012), it was discontinued in the VOICE trial as it was not found to be effective in preventing HIV among enrolled women (MTN 2011). Moreover, a gel-based product itself is not yet commercially available, while the TDF/FTC oral drugs are – and are therefore a product that could be used widely, once key implementation/delivery questions are answered.

An important result from recent clinical trials on oral PrEP has been the confirmation that PrEP works only if taken daily as prescribed (or nearly daily). In fact, the low levels of drug detectable in participants from the FEM PrEP and the VOICE clinical trials highlights precisely this issue: if the individuals taking the PrEP drugs are not sufficiently adherent to the prescribed protocols, then PrEP has no discernible effect in preventing HIV infections. How, then, can sufficiently high adherence be achieved and sustained? This is a key question for PrEP implementation and unfortunately, there are no ready-made answers. While quite a bit is known about how to measure adherence from studies of HIV treatment, and limited lessons do exist about promoting adherence from other health areas (including ARVs, TB treatment, treatment of hypertension and asthma) in a variety of country contexts, there is considerably less evidence about how to achieve high levels of adherence, particularly for preventive as opposed to treatment regimens. Experience with oral contraceptives has shown that on-going, daily adherence to a pill for prevention can be challenging.

The aim of the demonstration projects described herein is to aid in the design and measurement of the effect of interventions to promote and sustain adherence and to approximate the potential impact of including PrEP into combination prevention for HIV. In order to maximize the relevance and potential effect of these projects, several parameters must be considered.

First, PrEP is not envisioned to be a life-long prophylaxis. It is meant to be a choice among a number of prevention options, to be used for one or more specific periods in a persons' life, as and when appropriate. Therefore, retention on PrEP by itself is not an appropriate measure of programme

success – that is, going off PrEP is not necessarily a failure (unlike going off ART treatment, or not starting treatment), so long as other appropriate HIV prevention methods are used after PrEP is discontinued.

Second, any programme seeking to promote PrEP with high adherence needs to be shaped not only by available international evidence but by the particular country context: in equal part by the opportunities and limitations of the health system, and by the understanding of the behavioural dynamics of a client population (such as sero-discordant couples, men who have sex with men, young sexually active women, or others).

Third, the monitoring of safety and side effects is also a critical component of any PrEP demonstration project. Although the drug trials, to date, have not raised serious concerns about safety issues related to PrEP, acceptability of side-effects and medication toxicities1 (such as elevated liver enzymes, nausea and vomiting, headache, etc.) may be much lower among an uninfected population as opposed to an infected population which is deriving treatment benefit from the drugs. The tolerance of side effects and other potential safety issues for uninfected people may also be lower among health policy planners and providers. Careful monitoring of side effects is, therefore, essential for further ensuring the safety of PrEP, as well as for sustaining adherence.

Fourth, it is important to monitor the possibility of development of drug resistance among those taking PrEP who nevertheless acquire HIV infection. Current drug trial data suggests there is no association between taking PrEP drugs and the development of HIV strains resistant to these drugs, so long as an individual was correctly classified as HIV-negative at the beginning of the trial (Grant 2010; Baeten 2012). In other words, correct determination and careful monitoring of HIV infection status while taking PrEP is an imperative issue for PrEP delivery programmes.

Before PrEP can be made available as a prevention method, interventions designed to maximize PrEP adherence, monitor drug safety, and reduce chances of developing resistance if taking PrEP with unrecognized HIV infection must be tested at population-level, and in the context of the strengths and weaknesses of the health systems and the social contexts in which they will be provided – i.e., they must be tested in "real life" settings. The framework described herein attempts a challenging balancing act: informing initiatives that draw from and build upon local contexts and institutions, and yet have similar parameters and sufficient comparability to contribute to global lessons learned on how to promote and sustain adherence. Achieving adherence within the context and with the resources typically available in health care settings where routine care is provided will be a much different challenge from that seen in research settings.

Finally, the purpose of these PrEP demonstration projects goes beyond the scientific quest to design and evaluate interventions. The purpose is to assist the Ministries of Health (MOH) in countries which express interest to test models of service delivery that would have the potential to be implemented in routine programmatic settings. In other words, build a sustainable PrEP approach from the start, through five steps:

[1] Bone loss has also been tracked in the PrEP efficacy trials. While some limited bone loss has been found, it was not judged a serious safety issue. Measuring and monitoring bone loss will be beyond the scope of demonstration project research.

(1) Exploring and understanding context- and population-specific issues driving adherence, including issues related to the users' perspectives (such as confidentiality, barriers and facilitators to incorporation of the regimen into daily activities, occurrence and tolerance of side effects, perspectives on different methods of prevention, self- efficacy and gender relationships, etc.);

(2) Selecting and implementing components of a PrEP demonstration project most salient and realistic in a given country context, guided by a common implementation framework;

(3) Identifying the essential functions that a health system would need to develop and/or fulfil in order to sustainably implement a PrEP programme, including the necessary logistics of drug provision and dispensing, monitoring for safety and evaluation of effectiveness ;

(4) Carrying out an assessment, jointly with the health sector (i.e., Ministry of Health), about the readiness of the health system/sector to implement a PrEP programme, identifying obstacles and potential solutions;

(5) Carrying out a costing exercise for the intervention as a whole, and, as much as feasible, for individual programme components, including the potential integration of PrEP and treatment programmes.

This framework for protocol development, therefore, balances demonstration project research and implementation– i.e. the path between science and "real life." While it makes for a more complex project, addressing both research and implementation issues at the same time also means moving faster through the early learning stages of what works – and, hopefully, setting the stage for sustainability from the start.

II. PRIMARY STUDY POPULATIONS

The choice of populations to be covered by the PrEP demonstration programme should be based on assessment of greatest need (or greatest risk). Based on PrEP trials and PrEP guidance to date, these populations may include:

a. Sero-discordant couples (SDC), men who have sex with men (MSM) and sex workers (SW) in generalized epidemics
b. Men who have sex with men and sex workers in concentrated epidemics
c. Other high-need groups (such as mobile populations/truckers, etc.) in concentrated epidemics.

It should be recognized that these categories of individuals do not correspond perfectly with level of risk but are only a rough guide. Risk assessment tools may be needed to assess that level of risk in individuals and couples.

In addition, geographies of risk/need could be considered – that is, geographically-defined areas with high HIV levels, within which certain populations are at highest need (e.g., areas with high concentration of sex workers, mining settlements, etc.).
Additional research may also be needed among groups of people for whom PrEP has not yet proved successful (i.e. sexually active young women) to ascertain what other methods may help those populations to be sufficiently adherent.

III. PRIMARY OUTCOMES OF INTEREST

The two primary outcomes of interest for PrEP demonstration projects described here are: (i) the adherence to an effective prevention method (PrEP and/or other options from the country's combination prevention package); and (ii) the impact of that effort on HIV transmission. The first outcome will require careful monitoring of a number of key indicators. Most importantly, adherence must be well measured.

It is also very important to remember that retention on PrEP by itself is not an appropriate measure of programme success – that is, going off PrEP is not a failure (unlike going off ART treatment, or not starting treatment), so long as other appropriate HIV prevention methods are used.

A number of indicators of success must be tracked to measure those two primary outcomes in a population offered PrEP through a demonstration programme.

(i) Adherence to an effective HIV prevention method (PrEP and/or other options from the country's combination prevention package)

- When on PrEP, are users sufficiently adherent? While it is not completely clear at this time what that level is, careful measurement of adherence with possible laboratory confirmation will be important[2]
- What are the reasons for stopping PrEP? Making a distinction between reasons for stopping PrEP and assessing if they are associated with a change in prevention method or risk status, or are simply indicative of the failure to use PrEP will be important
- When not using PrEP, are other effective forms of HIV prevention being used?
- Are there changes in sexual risk taking behaviours?
- Is the person remaining HIV negative?

Suggested approaches to measure adherence to elements of combination prevention including PrEP are currently being elaborated and will be added to this document at a later stage.

[2] Additional research is ongoing to determine the target adherence level. The iPrEx study (Anderson, Sci Transl Med. 2012) indicated that 7 doses per week was likely associated with 99% efficacy.

For sero-discordant couples, the following elements may also be considered for measurement (refer to flowchart from the Partners Demonstration Project, Annex 1):

- Is HIV+ partner on ART, according to national guidelines, including undetectable viral load?

- Is the HIV- partner on PrEP or is he/she using another appropriate prevention method until HIV+ partner is on treatment and fully suppressed

For populations with concurrent sexual partnerships, the following composite indicator should be measured:

- Is PrEP being used in conjunction with another prevention method, especially condoms (by partner type)? This could equally be relevant to serodiscordant couples

This composite indicator is particularly relevant for female sex workers, where the use of condoms is paramount for additional protection they offer against other STIs as well as pregnancy. However, many SW also have regular partners, with whom condoms may not be routinely used – and hence the relevance of PrEP.

The main adherence indicators, their methods of measurement, and their strengths and weaknesses are listed in the table below.

- Note that pill counts are *not* recommended, because they are too labour-intensive and often an overestimate of adherence due to participant manipulation (i.e. pill dumping).

- Note that while adherence should be measured for all study participants, it is strongly recommended that a rigorous method of adherence measurement is used for a sub-set of participants in the demonstration project (i.e., either electronic monitoring such as MEMS Caps and/or blood testing for drug levels).

Indicator	**Methods**	**Strengths**	**Weaknesses**
For all populations			
Adherence to PrEP: maintaining at least 80% adherence among the population on PrEP regimen[3]	Self-reported adherence	Ease of measurement; low cost; particularly useful for individuals who report non-adherence, as it opens the opportunity for counselling, or switching to another method	Prone to over-estimating adherence due to self-report biases (recall bias, social desirability bias, etc.).
	Electronic monitoring (e.g. MEMS Caps)	Provides a longitudinal picture of adherence, allows for patterns of adherence (e.g. gaps of 1	Can be prone to tampering; cumbersome to use; expensive – so could be used for only a

[3] It is not yet clear whether 80% is the ideal goal. Additional research is ongoing to determine the best target level.

Indicator	Methods	Strengths	Weaknesses
		or more days) in addition to summary measures (e.g. means)	sub-set of study population
	Drug levels in blood	Most objective measurement of adherence (at one point in time); both intracellular (i.e., longer term) and plasma (i.e., shorter term) drug levels can be measured	Requires sophisticated laboratory capacity; invasive; expensive; could be subject to misreading (i.e. taking the pill prior to anticipated blood draw could result in "false positive") – so could be used for only a sub-set of study population
	Pharmacy (or clinic) drug refill for all subjects in study population	Ease of data collection (where the pharmacy/clinic set-up allows for it); non-expensive; has been shown to be a good predictor of adherence for ART	Provides a maximal estimate of adherence, which could be an overestimate if people do not take the pills they pick up (e.g. forgetting, side effects, sharing)
Reasons for stopping PrEP	Self-report on reasons for discontinuation, making a distinction between reasons associated or not associated with on-going risk (such as change to a known HIV-negative partner in the first case, as opposed to not being able to stay adherent in the latter)	Ease of measurement; inexpensive; particularly useful for individuals who report a specific barrier, as it opens the opportunity for counselling	Prone to various self-report biases (recall bias, social desirability bias, etc.)
When not using PrEP, using an effective form of HIV prevention (with particular focus on condom use)	Self-report for individuals who have discontinued PrEP during the demonstration phase	Ease of measurement; inexpensive (unless where it requires tracing of individuals)	Prone to various self-report biases (recall bias, social desirability bias, etc.). May be difficult to trace individuals who have stopped PrEP regimens and may not be in regular contact with health services.
Remaining HIV negative	Among individuals on PrEP regimen, data obtained through regular HIV testing, recommended every 3 months. Among individuals who are part of	For individuals on PrEP, data obtained through regular testing. Where available, oral testing can be used to minimize expense and invasiveness. Home testing may also be	Individuals who have enrolled in the demonstration programme but have stopped PrEP must be traced every 3-6 months throughout the project in order to conduct HIV

Indicator	Methods	Strengths	Weaknesses
	demonstration programme but not on the PrEP regimen, the HIV test could be at larger intervals (e.g., up to 6 months).	considered, but this is a controversial option	test. Prone to loss to follow-up. Providing incentives may be necessary for them to come back to the clinic.
Specific to sero-discordant couples			
HIV+ partner on ART, according to national guidelines	Clinic / HAART programme data	Data available through existing system	Linking data from a HAART programme and PrEP programme may be difficult in some settings
HIV- partner on PrEP (or using another effective prevention method) until HIV+ partner fully suppressed	PrEP adherence Use of other methods As in section "for all populations" above	As in section "for all populations" above	As in section "for all populations" above
Particularly relevant to populations with concurrent sexual partnerships, but applicable to all			
Dual use of condoms and PrEP.	Measuring/tracing both adherence to PrEP as well as use of condoms, as per methods described in above sections.	As in section "for all populations" above	As in section "for all populations" above

(ii) Modelled impact of the prevention effort on HIV incidence

Direct demonstration of public health impact of a PrEP component of a combination HIV prevention programme may be important for countries to justify continued inclusion of PrEP in national prevention efforts and guidelines. As stated earlier, the studies described by this framework will only be able to approximate impact given their limited size and duration. It will be possible however to use collected data on HIV retesting and adherence to PrEP and combination prevention to estimate HIV incidence of people participating in these studies. In many cases, estimates of HIV incidence among similar populations in the same areas will be known; these can be used as a comparator for the incidence figure derived from HIV retesting. In other cases, where estimates of HIV incidence may not be known, mathematical modelling can be used to derive a reasonable estimate of HIV incidence for a comparison population.

WHO will assist in identifying a partner institution which could assist in carrying out the modelling exercises, and help establish the relationship between the organisations conducting the demonstration project and the modelling institution (WHO contact on all PrEP related topics: Kevin O'Reilly, oreillyk@who.int).

IV. SECONDARY OUTCOMES OF INTEREST

a. Kidney function, as measured by estimated creatinine clearance calculated from height, weight, age, sex, and creatinine levels (recommended to be measured at enrolment in the demonstration programme, then every 6 months). Other markers of side-effects that might be tracked include ALT & AST, phosphorus abnormalities, and bone loss (although it should be noted that to date, RCTs have not found associations between PrEP regimens and markers of these additional side-effects).

b. Drug resistance: to be tested on any breakthrough infection (i.e., individuals sero-converting while on the PrEP regimen). Note that testing for drug resistance requires advanced laboratory capacity; however, as the number of breakthrough infections is likely to be very low, this capacity is not required on a large-scale.

c. Pregnancy/fertility intentions. Refer to section 7.6 for discussion of this topic.

d. Sexual activity/behaviour, when possible including biomarkers of sexual behaviour. Key behaviours must be selected as appropriate and feasible; the number is likely to be limited for reasons of feasibility. These may include partners (number, type, new) and sexual acts (type of sex with or without condom use). These data may be collected by various interview techniques, as has been the established practice is HIV prevention research. The biomarkers that have been found most useful are those for selected sexually transmitted infections. These can be obtained through routine screening and treatment (and/or symptomatic diagnosis) for these infections. The potential recommended list includes: incident chlamydia, gonococcal and trichomonas infections, early syphilis, and HSV-2). The most appropriate sexually transmitted infections to include will vary by locality and by population. These biomarkers are not likely to be useful among sero-discordant couples, due to generally low prevalence and incidence of STIs.4 Pregnancy may also be used as an indicator of sexual activity.

e. Selected factors from the users' perspective associated with promoting or inhibiting adherence, such as self-efficacy, agency, depressive symptoms, employment status, perceived social support, food insecurity, etc. Evidence suggests all of these are relevant in promoting (or inhibiting) adherence to treatment and may play a role in prevention as well (Mills 2006; Rustveld 2009; Nachega 2010; Ranak 2010; Reach 2011; Omeje 2011; Weiser 2011). Based on the experience of Partners PrEP (Haberer, IAPAC Adherence Conference 2012), sexual behaviour (e.g. outside partners, patterns of sex, risk perception), alcohol use, age, gender, and SES should also be assessed. Social support, quality of the partnership (if present), stigma, structural barriers (e.g. lost productivity to come to clinic), fertility intention, and perceived efficacy should also be measured as these are likely to be related to adoption and adherence to HIV prevention measures including PrEP.

[4] The Partners Demonstration Project is using periodic SMS surveys to report on daily sexual behaviour - daily SMS for the full duration of PrEP could result in survey fatigue and questionable data

V. LENGTH OF PROJECT

The time period for recruitment is to be defined in each specific setting and for each population. However, it is recommended that the follow-up period for a demonstration project is at least 12 months, preferably 18, if not 24 months. Individuals may use PrEP for a shorter period of time (e.g. the 6 months they are waiting for their partner to potentially become fully virally suppressed). However, as one of the primary outcomes of interest is the use of combination prevention including PrEP, and because sexual behaviour and/or social circumstances may change over time, it is recommended to follow all people for the whole length of the project.

VI. DEMONSTRATION PROJECT COMPONENTS

The components described herein represent the main areas to be considered for every PrEP demonstration project, given the specifics of the population of interest and the setting/context. The components are:

1. Recruitment
2. Initial HIV testing protocol
3. Supply of once-daily oral PrEP drugs
4. Adherence counselling
5. Monitoring of adherence, HIV status and safety
6. Additional/optional components to maximize adherence
7. Pregnancy and breastfeeding

6.1 Recruitment

The priority population for a PrEP programme will be defined in each location, as will the best methods to recruit these populations. Below are some general notes and considerations on recruiting some of the priority populations (there may be others, depending on the context).

1. Sero-discordant couples (SDC)

   - The SDC may already be in contact with the health system through the HIV+ partner; therefore, it may be relatively straight-forward to enrol the negative partner in prevention, assessing whether PrEP (or another method of prevention) is appropriate. Couples counselling specifically has been a good recruitment strategy for Partners PrEP. A link between counselling and testing sites, as well as treatment sites, and the PrEP demonstration programme could be established.

   - Consider whether all SDC are at equal risk (e.g., those intending conception, when the negative partner reports extramarital sex partners). Note that the Partners PrEP demonstration project will use a risk score (see Annex 2. Risk score composed of 6 different indicators, such as whether the couple is married, whether they have children, etc.), and will enrol only those who are considered at highest risk on the basis of the score (those with risk of HIV incidence of 5% per year or more, according to the score).

- Consider what happens if the couple breaks up. The HIV+ partner is likely to stay in contact with the health system, but this is less likely the case for the HIV- partner. It should be considered whether the HIV negative partner (who needs to be counselled on whether PrEP remains the optimal prevention method for him/her) should be followed through the demonstration project (to assess adherence to an appropriate HIV prevention strategy, and potentially, HIV status).

Recruiting MSM, SW, and "young women at risk" may be more challenging (as compared to SDC), as they do not tend to be in regular contact with the health system (with the exception of sex workers in some settings). Approaches to reach these populations might employ strategies outside of the clinic setting.

2. Men who have sex with men (MSM)

   - A PrEP demonstration programme will have to be creative (and context-specific) in finding the best venues through which to reach MSM. This could include STI clinics, school clinics, VCT clinics, centres which specialize in men's health, use of the web, etc.

   - Often, there are community-based organizations which work with MSM – if they are delivering some level of health interventions, it might be possible to deliver PrEP through these settings as well. It is also a good way to support their overall work on structural issues relating to MSM.

   - It will be very important to be aware/ mindful of legal issues around MSM when deciding where/how to offer services.

   - Note also that not all MSM are high-risk, so there may be a need to prioritize delivery of PrEP to a sub-set of the MSM community (e.g., using a risk score, or focusing on male SW,their clients, transgenders, etc.)

3. Female sex workers (SW)

   - Forthcoming qualitative FHI data from African settings suggests that SW prefer SW-focused services (other settings/SW populations might have different preferences). In such cases, these services could be considered for PrEP delivery (so long as they already provided some health services, otherwise it may be too intensive to build up capacity). However, these tend to be NGO or community-based organizations; in each setting, work must be done to ensure the government supports (or at least does not object) to delivery of PrEP through these services.

4. Young women at risk

   - In some settings, a PrEP demonstration programme could be nested in family planning (FP) clinics, although this would only reach the sub-set of women accessing those clinics.

- For adolescents, adolescent-friendly health services (where they exist) could provide an entry-point for a PrEP programme.

- To facilitate medication adherence, it will be very important to help women assess their own risk, as lessons from the FEM-PrEP RCT showed that risk perception among the general female population was very low.

- Demonstration programmes could make use of existing innovative approaches such as community based provision of contraceptives, which are commonly found across Africa, for eventual re-provision of PrEP after initiation and adjustment to PrEP in a clinical setting, for example.

6.2 Initial HIV testing protocol

When possible, it is recommended to follow the CDC protocol, which states that an individual must have a negative HIV antibody test (blood test), as well as no viral symptoms before being enrolled in a PrEP programme. If symptomatic at the evaluation visit or in the prior 4 weeks, tests to exclude acute HIV infection must be done. The box below is excerpted from CDC guidance.5 Note that although the guidance refers to men who have sex with men, the guidance is equally applicable to other populations.

CDC interim guidance for health-care providers electing to provide preexposure prophylaxis (PrEP) for the prevention of HIV infection in adult men who have sex with men and who are at high risk for sexual acquisition of HIV
Before initiating PrEP
Determine eligibility
• Document negative HIV antibody test(s) immediately before starting PrEP medication.
• Test for acute HIV infection if patient has symptoms consistent with acute HIV infection.
• Confirm that patient is at substantial, on-going, high risk for acquiring HIV infection[6].
• Confirm that calculated creatinine clearance is ≥60 mL per minute (via Cockcroft-Gault formula).
Other recommended actions
• Screen for hepatitis B infection[7]; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision about prescribing PrEP.
• Screen and treat as needed for STIs

[5] Centers for Disease Control. Interim Guidance: Pre-exposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men. January 28, 2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm?s_cid=mm6003a1_w

[6] In the case of the Partners Demonstration Project, 'high risk' is defined as 5+%. That may or may not be the right cut off, depending on populations, priorities, etc.

[7] Concurrent use with Hepatitis B infection is problematic

6.3 Supply of once-daily oral PrEP drugs

The supply interval (refill) of the PrEP drugs could be between 30 and 90 days, depending on the population group. It should not be longer than 90 days, as individuals on PrEP will also need an HIV test every 90 days. The refills can be halted in the case of (a) HIV sero-conversion, (b) adverse effects, such as abnormal renal function tests, (c) self-reported problems with adherence, (d) decision to stop PrEP by the individual following a change personal circumstances (no longer in a partnership with HIV+ partner, FSW has stopped selling sex, individual doesn't want to take PrEP anymore, etc.).

The location and mechanism of regular refills can be varied, depending on the refill interval and the specifics of each setting and population. In some settings, pharmacies may be optimal locations for refills (except the refills every 3rd month, which must be accompanied by an HIV test). Note that pharmacy refill is also considered a valid and robust proxy measure of minimum adherence – namely, a person picking up prescriptions regularly has the potential for complete adherence, although actual adherence behaviour may vary (see section 3, "Primary outcomes of interest"). When using pharmacy refill, consistent use of a single pharmacy system and tight control over pharmacy distribution systems is needed and electronic records represent a significant advantage.

Furthermore, every PrEP demonstration project must consider the ethical question of ensuring continuous access to PrEP drugs to individuals enrolled in demonstration project, after the project is finished (particularly in the case that PrEP does not become widely accessible, or affordable, for the population enrolled in the demonstration phase).

6.4 Adherence counselling

There is evidence suggesting that a multi-faceted approach to patient care, including comprehensive counselling, is effective in promoting medication adherence (e.g., Ngure et al, 2009; Chong 2011). On the other hand, it is in the interest of PrEP demonstration projects to mirror the real-life constraints of the settings in which they are implemented. Therefore, a balance must be found between the research-optimized and realistic levels of individualized care and counselling.

- Counselling will need to include PrEP medication adherence counselling as well as risk-reduction counselling (specifically addressing risk compensation – i.e., attempting to prevent PrEP from negatively affecting the use/adherence to other appropriate HIV prevention strategies, such as condom use). It will also need to go beyond PrEP medication adherence, to include adherence to an effective prevention regimen (such as correct and consistent condom use, mutual monogamy with a seroconcordant partner, etc.) that is well suited to the individual's needs and preferences.

- At the same time, it will have to be fairly time-limited, given the logistical constraints of time and personnel availability in most settings where demonstration projects will take place. E.g., The Partners Demonstration Project will provide thorough counselling at baseline, but plans to have counselling sessions of about 10 minutes in length for follow-up (as compared to the RCTs, in which the counselling was often 30-60minutes at each visit). Additional, more in depth sessions will be available as needed.

- Counselling needs to address the potential side-effects of PrEP, particularly gastro-intestinal issues, which tend to be more pronounced in the 1st month of taking the drug. This is to encourage clients to keep taking the drugs through these temporary side-effects.

- Other challenges seen in the Partners PrEP Study include alcohol use, relationship discord, outside sexual partners, travelling (often with longer than anticipated stays), and simply forgetting (especially with changes in routine). Other factors shown to be barriers to adherence to ART as treatment include food insecurity, transportation to pick up medication, stigma, and depression.

- Interactive, client-centred, problem-solving approaches (addressing barriers and facilitators to adherence) yield better results in promoting adherence; approaches which are too prescriptive and authoritarian yield poor results. CDC has described client-centred approaches for HIV testing and counselling. The principles may be useful for increasing adherence as well. For more information refer to the CDC client-centred counselling approach8.

- Most likely, some level of training of professionals in charge of providing the counselling will need to take place. For a demonstration project, it might be worthwhile to compare different counselling approaches – evaluate them by comparing adherence levels (e.g. drug levels).

- Checklists and manuals developed to promote adherence within PrEP RCTs are available and could be adapted for use in demonstration projects (e.g., Partners PrEP Study had concerted effort to intensively counsel those participants whose adherence was below 80% in the ancillary adherence study). These manuals, however, will not likely be practical for direct use in a demonstration project due to time and resource constraints. (Available upon request from Kevin O'Reilly, oreillyk@who.int)

- For SDC, counselling needs to include a component of initiating antiretroviral therapy for sero-positive partners once the nationally-defined eligibility criteria are reached.

- There could also be additional materials and/or interventions to support messages given in counselling – for example, take-home materials, peer educators, or adherence buddies. Among serodiscordant couples, the obvious helper is the partner. However, this model might (or might not) be translatable to other populations. Also to be noted, in some situations formalized treatment buddies can be a barrier to enrolment.

6.5 Monitoring of adherence and safety

As described in the section on Primary and Secondary outcomes, adherence is the main outcome of interest, and safety indicators the secondary outcomes.

[8] Centers for Disease Control and Prevention. Revised Guidelines for HIV Counseling, Testing, and Referral and Revised Recommendations for HIV Screening of Pregnant Women. MMWR 2001;50(No. RR-19).

- If electronic monitoring (e.g. MEMS Caps) is to be used, the demonstration projects needs to include: a) procurement of MEMS caps and associated software/hardware; b) training of health providers in the use of MEMS Caps, and in training clients in their use; c) a system managing and cleaning the data from the MEMS Caps (a secured on-line system is also available if internet access is reliable).

- If blood testing for drug levels is to be used, the demonstration projects needs to include: a) identifying sites where blood can be drawn, or dried blood spots collected, and a protocol for ensuring appropriately timed blood draws by the individual (in the case of Partners Demonstration Project, blood is drawn at each quarterly visit and banking/batching is for later testing); b) link to a laboratory with capacity to do the required testing; c) organization of timely results from lab to demonstration project to allow the use of the results. This may go beyond the scope of implementation to use drug levels. The turnaround time is slow, it is expensive, etc. This is a good research tool, but not practical for 'the real world. On the other hand, this data would be best used for data analysis. Also, untimed drug levels have been shown to be a pretty blunt measure of adherence for ART (Liechty, AIDS, 2004) but detection of no/low levels can be useful.

- Collection of hair samples is possible as well, as another method to assess adherence and duration of pill taking

- Regarding secondary outcomes (e.g., renal function as based on estimated creatinine clearance), these are to be assessed (tested for) every 3rd month, together with the HIV test.

An important consideration is how to address intermittent use of PrEP.

- While a person is taking PrEP, he/she should be encouraged and supported to follow a daily regimen. Intermittent use (i.e. coitally dependent dosing, set weekly dosing – eg: Monday, Friday and within 2 hours after sex -, etc.) should be discouraged.

- Experience shows that people who planned for intermittent use found it much more difficult than they thought. (See data from the IAVI pilot of intermittent PrEP. Mutua, PLoS One, 2012). PrEP users ought to be counselled that intermittent use is actually much more difficult to do accurately. It is best to plan for daily use, recognizing that an occasional dose may sometimes be missed since perfect adherence is not possible for most people, but that people should try their best in order to achieve optimal effectiveness from PrEP. Also, counselling should note that intermittent use gives very little "grace period" – since the drug levels in blood may not be adequate to protect against HIV acquisition.

- On the other hand, experience also shows intermittent use simply will happen. It is recommended that the PrEP programme be prepared for these instances. The main message to give PrEP users is that one pill is not enough to protect them, and that daily use is the goal they should strive for. The project should try to identify barriers to consistent use, and help the person address these for better adherence.

- In addition, PrEP counselling must include a component to explain what is known about possibly creating drug resistance and intermittent use: intermittent dosing will lead to drug levels that are potentially inadequate for HIV protection. If a person becomes infected, these low levels of antiretroviral drugs are not sufficient for viral suppression and may result in a virus that is resistant to tenofovir and/or emtricitabine).

6.6 Pregnancy and breastfeeding and PrEP

It is recognized that particularly among SDC, but also among other populations, PrEP may be an option for safer conception and during pregnancy. The FDA makes the following statement on the use of the PrEP drug TRUVADA and pregnancy: "TRUVADA has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that TRUVADA does not increase the risk of major birth defects overall compared to the background rate. There are, however, no adequate and well-controlled trials in pregnant women. Because the studies in humans cannot rule out the possibility of harm, TRUVADA should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking TRUVADA for a PrEP indication, careful consideration should be given to whether the use of TRUVADA should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy" (FDA 2012).

In regards to breastfeeding, FDA recommends that mothers should be instructed not to breastfeed if they are receiving TRUVADA, whether they are taking TRUVADA for treatment or to reduce the risk of acquiring HIV-1 because the risks of low level exposure to emtricitabine and tenofovir for breastfeeding infants are unknown.

The Partners Demonstration Project will be providing information to enable women to consent to continue with PrEP during pregnancy if they wish, noting higher risk of acquiring HIV infection that is present during pregnancy.

Given the above guidance, it is recommended that PrEP demonstration project include a sub-study, with separate consent, in which the decision to provide Truvada to pregnant women (or to those attempting to conceive) would be optional (up to each woman and her physician). Such sub-studies would need to follow pregnancy outcomes through 12 months (not just anomalies at birth). It should be noted that this component may be challenging for some PrEP demonstration project settings, as it also requires the creation of a registry for women and babies, a system to ensure they come back for follow-up, and trained personnel who is able to assess (i.e., paediatricians) infant outcomes.

6.7 Additional/optional components to potentially improve adherence

A PrEP demonstration project may consider, in addition to the above essential components, other elements described below which have been shown to increase adherence to ART and TB treatment. It should also be noted that motivations for prevention are different, so it is unknown if these interventions will have similar effects. They are topics for research within the demonstration, not proven interventions. In addition to implementing these in the demonstration phase, it should be considered whether such interventions would be sustainable and feasible on a large scale (e.g., national implementation).

1. Helpers/supporters for adherence

   - There is mounting evidence (e.g., Birbeck 2009; Ware 2009; Nachega 2010; O'Laughlin 2011; Kunutsor 2011) that treatment supporters – i.e., someone close to the client who can help remind & monitor adherence – can significantly improve adherence; this work has mainly been done in context of ARVs, some also in context of TB treatment.

   - Among sero-discordant couples, the first choice of helper would be the partner (building on the Partners PrEP Study, where it was found that partners "naturally" fill this role for each other. See also Ware, What's Love Got to Do with It, JAIDS 2012, which deals with PrEP adherence specifically), although it wouldn't have to be the partner. Most often, the supporter is chosen by the client – e.g., a family member, a friend, etc.

   - The role of the helper needs to be well defined. Being a helper must be at least a semi-formal function, whereby the helper must (a) receive some training in what it means to be a helper, (b) pledge to fulfil the role, (c) have specific recommendations as to what he/she can do – i.e., when/how/how often to check on the client, what to do to encourage adherence, what to do if non-adherence is suspected, and an exit strategy.

2. Reminders/tools for adherence

   - There is evidence that mobile phone reminders (SMS or phone calls) can be effective in promoting adherence to ARV treatment (Horvath 2012; Pop-Eleches 2011). The appropriateness and feasibility of such approaches needs to be assessed in each setting of a PrEP demonstration project.

   - If not using MEMS caps, pill boxes and small travel cases (e.g., that fit on a key chain) can be useful. Adherence to PrEP should not be sacrificed for the sake of measurement. That is, if an individual does not want to use MEMS, study enrollment (or sub-study enrollment) may not be appropriate. If the participant is ok with MEMS most of the time, but does not want to use it for discrete periods of time (e.g. a weekend trip), a travel case could be used and documented for adjustment of the MEMS data. Such adjustments can be problematic, however, because they rely on self-report

3. Incentives for adherence

   - A review of incentive-based health programmes in the UK (Sutherland 2008) found that "patient incentives can be effective in helping to secure simple, well defined episodes of behaviour change (for example, vaccinations and cancer screening). However, for complex and sustained behaviour change there is insufficient evidence to declare that patient incentives are effective as quality enhancing interventions." It also found that "where direct costs are perceived to be a barrier to behaviour change (for example, transportation costs, cost of nicotine replacement therapy), offsetting those costs can contribute to behaviour change in motivated patients." It should be noted that monetary incentives are not likely to be sustainable in implementation, so there may not be a great role for them in

demonstration projects. Transportation refunds may have more potential, but again, there is likely to be an issue of sustainability with such incentives.

- As was observed in iPrEx, some participants expressed their satisfaction in being part of a group with shared concerns, in which their experience and efforts are validated and they were treated with respect. It is therefore possible that the incentive and motivation for some participants is the possibility to belong to a group where their experiences and needs are heard and taken seriously. Therefore, setting up client support groups, or similar, might be a way to incentivize participants.

4. Influencing group social norms to support adherence

- The best way to influence social norms depends on the target population, but usually involves working with "opinion leaders" and/or role models so they become advocates of the cause.

- The term "opinion leader" usually refers to a person from the target population who has a lot of social influence/clout; this works best for fairly narrowly defined populations and groups (e.g., different MSM sub-groups, CSW groups, etc.). Working with opinion leaders involves education, motivation and communication interventions targeted at the leaders, and then a campaign component to "kick off" the new trend. This remains fairly small-scale and personal – the idea is for the opinion leader to spread the norm in his/her immediate group of influence. (Note: in well-defined/closed groups e.g. sex workers, this model works well)

- Role models do not have to be part of the target population but are someone that the target population admires/looks up to (e.g., public media figures, popular politicians, etc.). Working with role models usually involves a media campaign where the role model lends his/her image/voice to the cause. This is usually large-scale and impersonal.

- There are also other types of influential people who can sometimes be brought to a cause, such as religious leaders, chiefs/elders, etc. If convinced of the cause, they can highlight an issue and put their weight/influence behind it. The scale of this type of work is "medium" (as compared to opinion leaders & role models) in that influential persons (sometimes also called "gatekeepers") are figures of local importance/prominence.

VII. STUDY DESIGN AND SAMPLE SIZE

As noted earlier, it is the intent of these demonstration projects to demonstrate the feasibility of delivering a combination prevention program which includes PrEP, ensuring sufficiently high adherence levels when PrEP is used, and estimating the potential impact on HIV transmission. PrEP impact on HIV transmission should be mathematically modelled using uptake, adherence, retesting and average duration data collected in demonstration projects, coupled with efficacy data from the PrEP trials and epidemiologic data from the demonstration project areas.

The precise study design is to be decided for each specific setting and population, considering the following parameters:

- For the primary research question of whether PrEP can be delivered safely and effectively, an observational study is sufficient to answer this. For the estimation of impact, a comparison between the observed rate of infection on retesting for those using combination prevention including PrEP and the observed, estimated, or modelled HIV incidence in a similar comparison population will be necessary.

- A staggered implementation design, or a stepped wedge design, may well be feasible and may provide additional information to a country, though its use would be optional in this design – that is, a selection of regions or groups which will all receive the PrEP intervention within a given time period, with some receiving it before others. Before deciding to use this design, countries should clearly identify which questions will be answered by its use

- Research could also compare different additional PrEP components – e.g., comparing a PrEP programme which includes an "adherence helper" with one that does not, etc.

- If different models of PrEP delivery will be tested, it is critical to ensure that all the models include the essential components (as described in sections 6.1 – 6.6, above). It is only the additional components which can be varied (as described in section 6.7), or, in some cases, different ways of delivering an essential component (e.g., different approaches to adherence counselling).

- Considerations need to be made for urban vs. rural sites, and for other distinguishing characteristics in each setting; sampling needs to take these variations into account.

- Sample size calculations will need to be performed for each setting and population, however, as a rough estimate, at least 600-800 individuals would be needed for each demonstration project group. If individuals will be followed over time (linking their data over time), then sample sizes may be smaller. For sub-studies (e.g. MEMS or drug levels), sample sizes may also be smaller.

VIII. ADDITIONAL RESEARCH TO EXPLORE USERS' PERSPECTIVES ON ADHERENCE SPECIFICALLY, AND PREVENTION APPROACHES MORE BROADLY

Every PrEP demonstration project ought to implement a number of related research components (qualitative and/or quantitative in method), covering areas which are essential for understanding and scaling-up PrEP delivery, and which could also inform future prevention approaches (e.g., topical PrEP, etc.). The main categories of interest are outlined below, although there may well be others, more relevant to a specific context and population.

- Qualitative research in the early phase of the demonstration projects, particularly to understand how much opposition/resistance there might be to PrEP, and finding best ways to address this. Importantly, those disagreeing with PrEP need to be included in the qualitative research (at policy, service delivery, individual and activist levels) – as it will be important to get their perspectives on how to do comprehensive prevention "the right way."

- Quantitative or qualitative research into sexual behaviour of the population of interest, to establish the need and appropriateness of PrEP. For efficiency sake, a literature review might be useful, as some populations may already be well characterized in some settings.

- Quantitative or qualitative research into potential facilitators and barriers to adherence (refer to the suggested list in section 4e). These findings could help to also guide the content of the counselling provided.[9]

- Quantitative or qualitative research into the perspectives of providers and the wider health system to understand barriers to delivering PrEP and comprehensive prevention, and ways to address these barriers.

- Tracking of drug sharing (qualitatively and/or quantitatively). The evidence available suggests that drug sharing is limited (e.g., iPrEx reported about 2%; FEM-PrEP reported very limited drug sharing; Partners PrEP doesn't have data available yet). However, since little is known about this phenomenon and behaviour may change outside of clinical trials and in the setting of known efficacy, demonstration projects should consider whether to attempt to assess it. This may occur among persons prescribed PrEP or persons receiving antiretrovirals for treatment. Tracking of drug sharing should occur in both populations.

- Consider whether the additional research could be longitudinal; that is, interviewing participants over the span of the project to track, over time, their experiences with PrEP, issues in their life that influence adherence, interactions with the health system and their effects on adherence, their individual social context and changes occurring within it, etc.

- In addition (or instead of qualitatively tracking individual participants), community monitors or community representative panels could be set up and followed over time to assess the same issues (e.g., experiences with PrEP, issues in life that influence adherence, etc.). "Community" would be defined as the client community.

[9] Studies ought to try to build on findings from Partners PrEP about adherence patterns, as reported at CROI (Donnell 2012): Among participants which started with undetectable drug, generally they continued to have non-detectable drug levels throughout the study; those with low levels of drug tended to stay in that category. Of those who started with high levels of drug, over half continue with high levels through the study; some stop dosing altogether (includes pregnancy), and there are some who have a single visit with low levels (i.e., one dip), then return to high levels. Behavioural and other risk and protective factors data could be correlated with such adherence trends to examine what are the main "drivers" of adherent behaviour as well as what events in a persons' life act as barriers to adherence.

- A literature review of HAART treatment adherence by gender found that women were generally less adherent than men (Puskas 2011). On the other hand, the Partners PrEP Ancillary Adherence Study found that men were less adherent than women (Haberer 2012). Therefore, demonstration projects would do well to examine the facilitators and barriers of adherence by gender (for relevant populations), and to use these findings to tailor individualized approaches (e.g., counselling).

- Note that qualitative research could also be part of the overall evaluation strategy of the comprehensive prevention intervention.

IX. ETHICAL CONSIDERATIONS

Demonstration projects on PrEP should adhere to all principles of the ethical conduct of research, including confidentiality of all participants' data, signature of informed consent when applicable, data protection, etc.

X. PrEP INTERVENTION AS PART OF A SYSTEMS-WIDE ANALYSIS: AIMING FOR SUSTAINABILITY

Since we do not yet know enough about how to ensure adherence to PrEP, the projects outlined herein must be "demonstration projects" – that is, small research projects taking place in real-life settings, but augmented, by a greater or lesser extent, by external factors (e.g. free PrEP drugs, availability of training materials, extra funding for training, etc.) in order to deliver the entire project "package" and in order to study the effects of this package on PrEP adherence. In other words, we need to first gather evidence about how to implement successful PrEP interventions before suggesting to health systems in relevant countries that they implement the interventions on a large scale. At the same time, it is clear that the most useful evidence will be grounded in the reality of existing health systems, and that working jointly with the health system from the early stage will be beneficial for eventual uptake of PrEP on a larger scale. Therefore, these demonstration projects include three additional steps:

1. Identifying the functions/services that a health system (including government & private providers, NGOs, etc.) at all levels – national, regional, local, and facility-level – would need to implement the components of a PrEP programme
2. Carrying out an assessment, jointly with the health sector (i.e., Ministry of Health), about the readiness of the health system/sector to provide PrEP, identifying obstacles and potential solutions
3. Carrying out a costing exercise for the programme as a whole and, if possible, for individual programme components. This needs to be done once a model for implementation has been developed and shown feasible and successful, acceptable and effective.

In doing so, we hope to avoid a scenario where considerations for "scaling up" are only considered at the end of the project as an afterthought. Instead, we aim to assist the health system in preparing to

incorporate PrEP into routine service delivery: scaling up through institutionalizing the necessary capacities for service delivery, i.e. including policies, norms, operational guidelines and budgets (institutionalization or vertical scaling up), while at the same time beginning to promote expansion of service availability (horizontal scaling up).

Step 1: Table 1 below identifies the generic functions that a health system would need to develop and maintain (and health workers perform) to provide PrEP interventions as part of an HIV preventions programme.

Functions of health system at national/regional level (depending on country):	
• Creating awareness and political support for PrEP	
• Purchase of PrEP drugs, commitment to minimum quantities over time	
• Incorporation of PrEP drug supply into existing supply systems (if adequate), or ensuring supply through other means	
• Incorporation of standards for delivery of drugs to clients into existing health care operational standards and monitoring mechanisms, if adequate; or creation of new standards and monitoring mechanisms (including, if relevant, private sector pharmacies)	
• Funding and supplies for HIV testing, and for renal function testing for clients on PrEP	
• Curricula development, funding (organizing) information-education trainings of health-care providers, counsellors, supervisors, managers. Funding (organizing) training of health providers (and, if relevant, pharmacists)	
• Incorporating PrEP into health insurance mechanisms	
• Consider integration of PrEP into ART and other HIV prevention programs (i.e. avoiding a siloed vertical approach)	
Functions of health system at regional/local level (depending on country):	
• Monitoring drug flow from national through regional levels, to facility levels (and, if relevant, pharmacies). Collating monitoring data from institutions; reporting to higher levels (if systems not automated)	
• Monitoring quality issues “down” the systems pipeline (i.e., facilities, pharmacies); reporting “up” the pipeline (i.e., regional or national level)	
• Organizing and implementing trainings for managers	
• Organizing and implementing trainings for health care providers (and possibly pharmacists)	
• Implementation of awareness/demand-raising activities among target population (NOTE: this function is in many settings this may be carried out by NGOs or other civil-society organizations)	
• Consider integration of PrEP into ART and other prevention programs (i.e. avoiding a siloed approach)	

Functions of health institutions (possibly also pharmacies):	
• Storage, availability of PrEP drugs & other supplies needed in the provision of PrEP (i.e., HIV tests, contraceptives, etc.)	
• Commitment to intervention/project, buy-in of standards	
• Use/application of monitoring mechanisms, including data reporting	
• Support & maintain trained providers	
• Monitoring of providers	
Behaviours of health providers (to be determined which, if any, relevant for pharmacists):	
• Individualized/client-centred risk assessments, effective counselling on adherence assistance to clients in development of adherence plans	
• Comprehensive HIV prevention counselling	
• Family planning counselling and provision of contraceptives	
• HIV testing, renal function testing (either on-site testing or sending specimens to labs, reviewing results and appropriate follow-up)	
• Case management function: following PrEP clients over time, reviewing adherence plans, support to treatment helpers Follow-up/management (or referral) of adverse events, making other appropriate referrals	

Step 2: An assessment about the readiness of the health system/sector to provide PrEP, coupled with a rapid assessment of target group members needs and perspectives, as well as broader community members perspectives regarding PrEP, identifying obstacles and opportunities and recommending potential solutions. This is to be carried out with the leadership and participation MOH, and can be modelled on WHO Strategic Assessments for strengthening reproductive health policy and programmes10. In these assessments, a multidisciplinary team representing a range of relevant stakeholders conduct a field-based assessment through observations of service delivery sites at multiple levels of the health system, coupled with in-depth interviews with policy makers and program managers, service providers, clients utilizing services, and potential high risk individuals who might use PrEP, as well as other community members and leaders. The goal of the assessment is to both make recommendations about how PrEP services should be organized and implemented in the national or sub-national context, for testing in the demonstration project, but also to begin to build support and consensus among stakeholders for the future implementation of the interventions, should they be proven feasible, acceptable and effective.

Step 3: The costing component needs to be developed. The institutional analysis and preparation, as well as costing exercise, are an integral component of the project. Although not commonly part of a demonstration project, this component is a key element in ensuring commitment and eventual uptake and implementation of PrEP on a large (national) scale, if deemed appropriate. These steps

[10] http://www.who.int/reproductivehealth/publications/strategic_approach/RHR_07.7/en/index.html

are in place to ensure that a PrEP interventions are developed within – or at least in dialogue with – the health system from the start. As a result, this process is meant to create national ownership of and investment into PrEP, to "prime" the system by identifying opportunities and potential roadblocks (and solutions) for national PrEP implementation.

Designing a PrEP demonstration project for future scaling up success

All too frequently pilot, demonstration and implementation research projects are successfully completed but then fail to be scaled up or to influence national policy and programme implementation. There are many reasons for this failure but a common problem with many projects is that they are focused on what is analogous to "proof of concept" in biomedical or clinical studies. They are testing whether interventions are likely to succeed if they are appropriately implemented. Therefore they provide special resources and support that are needed to ensure proper implementation in a research context. While such "proof of concept" studies may be initially necessary, there is a need from the outset to also be concerned with a "proof of implementation" -- learning whether interventions can be successfully implemented not only in a pilot with special resources, but whether they are feasible, acceptable, effective, and efficient when implemented under routine conditions in a large-scale programme. In recent years considerable attention has been given to the issue of how the results from research and demonstration projects can be more successfully transferred, and how considerations for successful future scaling up can be built into the design of these projects from the outset.

WHO's Department of Reproductive Health and Research, together with the network ExpandNet has developed guidance to facilitate this entitled, "*Beginning with the end in mind: designing pilot projects and programmatic research for successful scaling up"*[11]. This tool is intended to assist those designing demonstration or implementation research projects to think ahead and build considerations for scaling up into their research project designs. The document contains twelve recommendations intended to help project managers, those tasked with developing proposals and others to think ahead to how successfully tested innovations can be put into practice on a large scale. Each of the 12 basic recommendations is accompanied by a series of concrete actions to be taken in designing a pilot project. In addition there is a checklist at the end of the document to help review the proposal with regard to the recommendations during the process of proposal development and review. The recommendations can be summarized as follows:

1. Engage in a participatory process involving key stakeholders

Stakeholders who have been involved in the pilot are more likely to support its scaling up than those who had little input. Engaging future implementers and those who represent the beneficiaries is likely to produce interventions that are relevant, acceptable, appropriate, feasible and sustainable. Key actions include:

- Assessing who are relevant current and future stakeholders, seek their input on the design of the project, and plan to obtain their feedback on the process of implementation; and in particular

[11] http://www.who.int/reproductivehealth/publications/strategic_approach/9789241502320/en/index.html

- Include on the research/planning team key individuals from the future implementing organization(s) as well as beneficiary communities

2. Ensure the relevance of the proposed interventions

New innovations should be based on sound evidence and promise improvements in access, equity effectiveness and efficiency compared to existing approaches.

Most project managers or researchers will claim that the interventions they test are relevant – however it is important to couple relevance with feasibility. Interventions which are theoretically relevant but not feasible from an implementation point of view are not relevant for the health system context.

3. Reach consensus on expectations for scale-up

Expectations for scaling up may differ with regard to geographic areas for expansion, the level of service delivery, the beneficiary populations or the pace for scaling up. It is important to clarify what expectations for scaling up are among various stakeholders so that project design can reflect these expectations.

4. Tailor the interventions to the socio-cultural and institutional settings

It is important to design interventions in such a way that they are consistent with community and beneficiary group's values and social institutions. Likewise, a good match with the organizational culture of the health-service-delivery system is important. In addition, the larger political, economic, policy, bureaucratic and institutional environments need to be considered, to identify both opportunities and constraints for future scaling up. Specifically, the project team should:

- Identify community, socio-cultural and gender factors that might support or constrain implementation of the innovation
- Understand the norms, values and operational culture of the future implementing organization
- Assess opportunities and constraints within the political, policy, health-sector and other institutional environment that will impact future large-scale implementation; and incorporate the results in the design of the project

5. Keep the interventions as simple as possible

The simpler the interventions, the more easily they can be implemented in the future. All proposed components should be reviewed, examining whether they are essential and how the overall package can be kept simple while still having a reasonable expectation of success. Remember that the complexity of the innovation must match the capacity of the implementing organization, unless capacity-strengthening is part of the project.

6. Test the interventions in the variety of socio-cultural and institutional settings where it will be scaled-up

Testing the interventions in the local contexts in which they will be scaled-up seems obvious- but not always done. For example, if the objective is to introduce PrEP services for MSM, they should be

tested MSM seek health services. If nationwide implementation is the goal and the country is culturally diverse, piloting should involve as many diverse regions and geographic areas as feasible. It is also important to conduct the project in the institutions and the types of service delivery points that are expected to scale-up the interventions if they are proven successful. Interventions intended for implementation at health centres or at the community-level should be tested at those levels and not just in the district hospital.

7. Test the innovation under the routine operating conditions and existing resource constraints of the health system

Pilot projects often succeed because the innovation is implemented with special human, financial and technical resources that are not always available for large-scale implementation. Testing in the day-to-day operational realities, and within the resource constraints of the health-service system, is therefore essential. If an innovation cannot be implemented within the existing capacity of the health system then health system capacity building activities should be part of the package of interventions being tested

8. Develop plans to assess and document the process of implementation

Documenting what steps were taken to achieve results will help determine what needs to be done to implement interventions on a larger scale later on. Data is often collected about inputs, outputs and outcomes, but documentation and assessment of the process is also important for scaling up strategy development. Data on the implementation process include information regarding the inputs needed to ensure quality of care and required human resources and worker skills, as well as information on management issues such as leadership, supervision, incentive structures, costs, financing, logistics and the functioning of the management information system. Of particular importance is to determine the costs of implementation and costs to users; this is often overlooked and is critical for planning future scaling up

9. Advocate with donors and other sources of funding for financial support beyond the pilot stage

Process of scaling up is not routine implementation and needs special attention and support. Financial support typically stops with the completion of the pilot project. Successful innovations often fail to be scaled-up because the necessary financial resources to support scaling up have not been obtained.

10. Prepare to advocate for necessary changes in policies, regulations and other health-systems components

Successful scaling up of innovations often requires changes in policies, laws, regulations, budgets, standards, service protocols and other health-systems components. Although the process of institutionalization typically has to wait until the project demonstrates the desired results, planning to take steps to initiate these necessary changes should be part of the project-design process.

Specifically, the project team should plan to:

- Assess what changes in policies, norms, regulations or other health-systems components are needed to institutionalize the innovation

- Explore institutional timelines, procedures and formal as well as informal processes required for the necessary change
- Initiate policy discussions about these potential changes with relevant decision-makers

11. Develop plans for how to promote learning and disseminate information

The process of implementing a project provides multiple opportunities for learning. Many insights will emerge about what works, when and how. While safeguarding the need for robust evidence, it will be important to adjust the innovation where necessary as testing proceeds or circumstances change, and to adapt measurement and documentation accordingly. Piloting is not only testing and demonstrating a model but also refining it through an on-going learning process.

- Promote observability of the innovation by taking stakeholders to visit pilot sites
- Commit to periodic reviews as implementation progresses in what is likely to be a changing social, political and institutional environment
- Make necessary changes to incorporate learning about how implementation can be improved
- Adjust data collection when necessary
- Document the changes in the package of interventions that are being made and the reasons why

12. Plan on being cautious about initiating scale-up before the required evidence is available

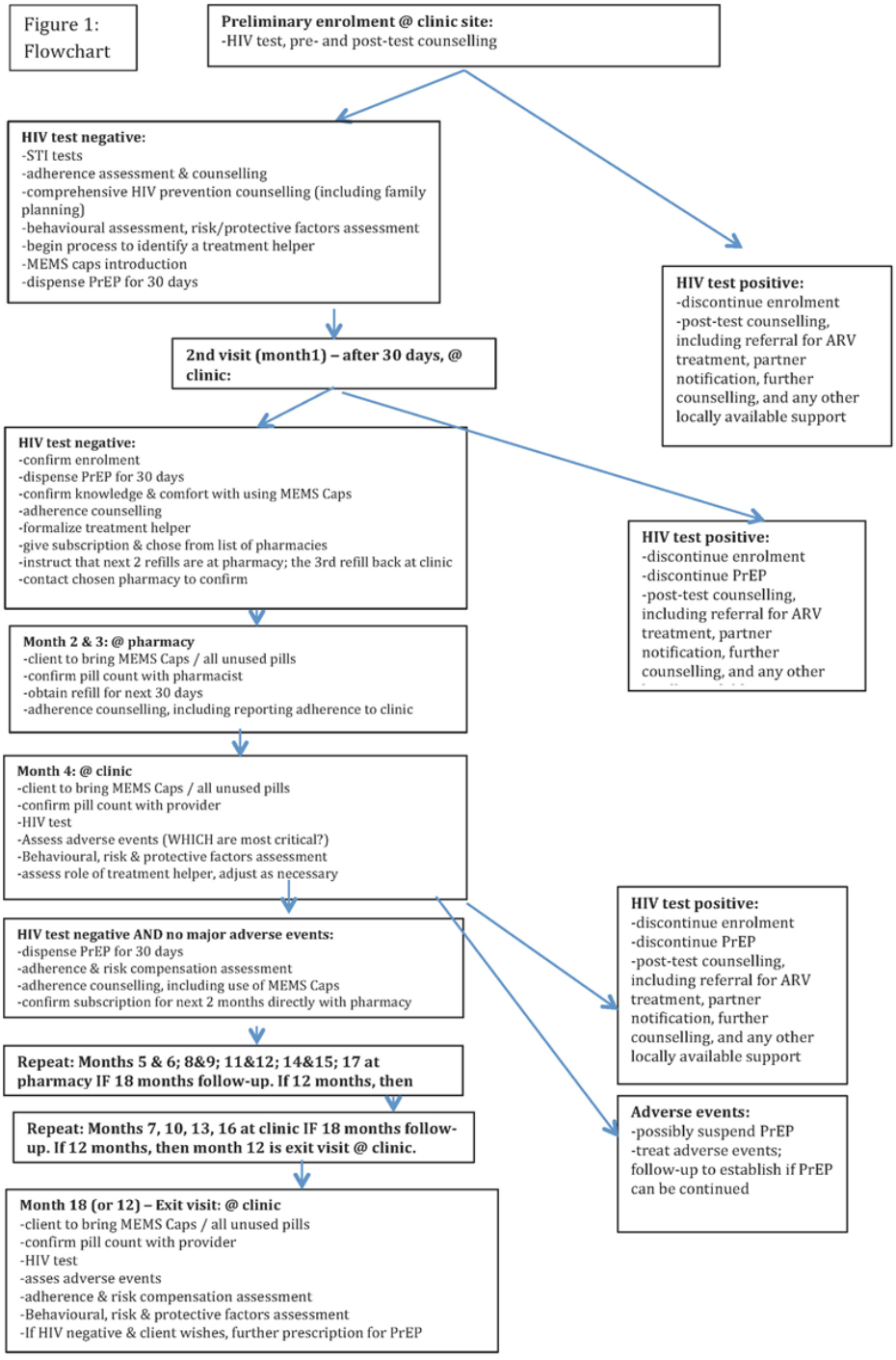
Promising initial project results often lead to pressure to scale-up the innovation before its feasibility and outcomes have been fully demonstrated. Proceeding without sufficient evidence can lead to scaling up interventions that do not work or require further refinement. It is therefore important to plan on being cautious about premature scale-up.

Putting these recommendations into practice in the process of proposal development will not guarantee later scaling up success-- it will still be necessary to develop an appropriate scaling up strategy and of course to mobilize financial and managerial support for the process. However, beginning with the end in mind will put the demonstration of the right path to future success in scaling up.

ANNEXES

Annexe 1: Flowchart on Indicators from the Partners Demonstration Project

(Note: Provided as an example. Some elements of this flowchart will not be applicable for other populations or other settings)



Annex 2: Risk scoring tool from the Partners PrEP Study Demonstration Project

Figure 3. Risk scoring tool

Age of HIV-1 uninfected partner		
	20 years or less	4
	21-30 years	1
	More than 30 years	0
Number of children		
	0	2
	1-2	1
	3 or more	0
Male HIV-1 uninfected partner uncircumcised		
	Yes	1
	No	0
Married and/or cohabiting		
	Yes	1
	No	0
Unprotected sex within partnership, prior 30 days		
	Yes	2
	No	0
HIV-1 plasma viral load, HIV-1 infected partner		
	50,000 copies or higher	3
	10,000-49,999 copies	1
	Less than 10,000 copies	0
Total score *(≥5-6 = higher risk)*		

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