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