

## Chapter 2

# Translating Pre-Exposure Prophylaxis Evidence into Practice and Public Health Impact

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For the first 29 years of the HIV epidemic, there were only five randomized controlled trials that demonstrated an impact on reducing HIV incidence. They were studies of medical male circumcision in South Africa [1], Kenya [2], and Uganda [3], a trial on treating sexually transmitted infections in Tanzania [4], and the RV144 HIV vaccine trial conducted in Thailand [5]. However, over the past 2 years, results from five randomized trials have provided compelling evidence that antiretrovirals (ARVs) can prevent sexual transmission of HIV. The first in a series of trials showing that ARVs can reduce HIV acquisition was the CAPRISA 004 tenofovir gel trial. This trial, conducted among 889 rural and urban South African women, showed that tenofovir gel used before and after sex reduced acquisition of HIV infection in women by 39 % (95 % confidence interval (CI): 6;60) overall, thereby providing the proof-of-concept that ARVs can prevent sexual transmission of HIV [6]. Soon thereafter, the results of the iPREX trial were announced, which showed that the daily oral tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) combination (Truvada) reduced HIV incidence by 44 % (95 % CI 15;63) among 2,499 men or transgender women who have sex with men [7] (Fig. 2.1).

Further evidence for the effectiveness of daily oral pre-exposure prophylaxis (PrEP) in heterosexual men and women comes from results of the Partners PrEP

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### Study

Partners PrEP – daily Truvada  
(Discordant couples – Kenya, Uganda)

Partners PrEP – daily Viread  
(Discordant couples – Kenya, Uganda)

TDF2 – daily Truvada  
(Heterosexuals men and women- Botswana)

iPrEx – daily Truvada  
(MSM - America's, Thailand, South Africa)

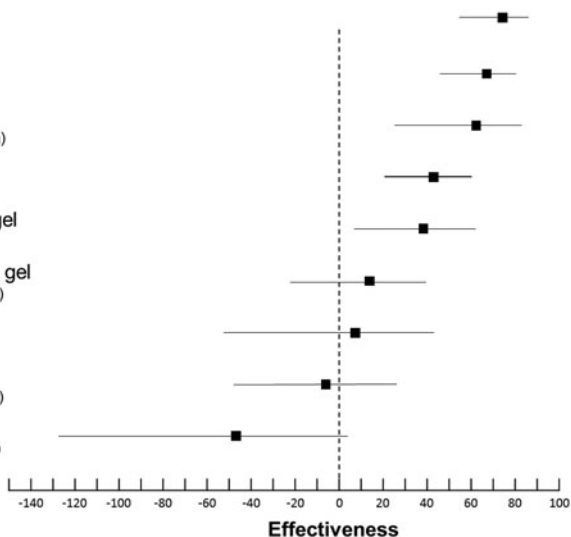
CAPRISA 004 – coital Tenofovir gel  
(Women – South Africa)

MTN003/VOICE – daily Tenofovir gel  
(Women – South Africa, Uganda, Zimbabwe)

FEMPrEP – daily Truvada  
(Women – Kenya, South Africa, Tanzania)

MTN003/VOICE – daily Truvada  
(Women – South Africa, Uganda, Zimbabwe)

MTN003/VOICE – daily Viread  
(Women – South Africa, Uganda, Zimbabwe)



**Fig. 2.1** Results of pre-exposure prophylaxis effectiveness trials

trial [8] and the Botswana TDF2 trial [9]. The Partners PrEP trial, which included 4,758 HIV-discordant couples from Kenya and Uganda showed that daily oral TDF and TDF/FTC reduced HIV incidence by 67 % (95 % CI 44;81) and 75 % (95 % CI 55;87), respectively, whereas the Botswana TDF2 trial, conducted among 1,200 heterosexual men and women from the general population, found that daily oral TDF-FTC reduced HIV incidence by 62 % (95 % CI 22;83; Fig. 2.1).

The use of ARVs for treatment of HIV-infected patients has also recently been shown in a randomized clinical trial to prevent onward transmission of HIV to their uninfected partners (Treatment as Prevention—TasP). The HPTN 052 trial, conducted among 1,763 HIV-discordant couples from nine countries, showed that HIV transmission was reduced by 96 % (95 % CI, 73;99.5) when ART was initiated in patients with CD4 counts between 350 and 550 cells/mm<sup>3</sup> [10].

This series of scientific breakthroughs in HIV prevention, combined with the recent approval of the first antiretroviral drug (Truvada) for reducing the risk of sexually acquired HIV infection by the US Food and Drug Administration (FDA) [11], has made the use of antiretroviral drugs as part of a comprehensive HIV prevention package, a reality and has created newfound hope that the epidemic can be stopped. This unprecedented opportunity to alter the course of this disease will depend on the extent to which regulators, health service providers, funders, and researchers are able to translate this new evidence into effective large-scale treatment and ARV prophylaxis programs.

## **Implementation of Biomedical HIV Prevention Technologies: Potential Impact**

Significant prevention benefits have been shown to be possible with the implementation of the “test and treat” strategy, where all individuals who test HIV positive are immediately initiated on antiretroviral therapy, irrespective of CD4 count [12]. Several mathematical models have produced impressive estimates of the potential prevention impact of universal testing and immediate antiretroviral treatment. In rural KwaZulu-Natal in South Africa, scale-up of the routine AIDS treatment program has shown an impact on HIV incidence at community level. A population-based prospective cohort study, which included 16,667 individuals who were HIV-uninfected at baseline, showed that the risk of HIV acquisition between 2004 and 2011 was 38 % lower in communities where 30–40 % of HIV-infected individuals were on ART compared with communities where less than 10 % of the HIV-infected population were on ART [13].

The provision of PrEP to avert new HIV infections needs to be weighed against the potential costs of providing life-long ARVs for individuals who may become infected with HIV. Several mathematical models have illustrated the potential impact of oral and topical PrEP on the epidemic trajectory. Up to 3.2 million new HIV infections could be averted in southern sub-Saharan Africa over 10 years by targeting PrEP (having 90 % effectiveness) to those at highest behavioral risk [14]. Similarly, mathematical modelling has shown that in South Africa alone, over the next two decades, tenofovir gel could avert 1.3 million new HIV infections and over 800,000 deaths [15]. Mathematical models have also shown that oral and topical PrEP is cost effective [15–17].

Although medical male circumcision took some time to be incorporated in the HIV prevention package, widespread implementation of this HIV prevention technology is already having a population-level impact. In Orange Farm, South Africa, the male circumcision rate has increased from 16 % in 2007 to 50 % in 2010 and has been shown to be associated with reductions of 55 % in HIV prevalence and 76 % in HIV incidence [18].

## **Regulatory Obstacles Restricting Access to Biomedical Technologies Such As ARVs for HIV Prevention**

Despite the potential impact of PrEP, only the US FDA has officially approved Truvada as an HIV prevention option. This led to the development of guidelines for its use in men who have sex with men [19] and in heterosexuals [20]. Since Truvada has not been approved by medicines regulators in any other countries, country-specific individual patient guidelines and programmatic public health guidelines on implementation of PrEP cannot be developed.

## Challenges in the Implementation of PrEP

Besides the regulatory hurdles and lack of country-specific guidelines, several other challenges could impact on the rapid implementation of PrEP. Although mostly unwarranted, the main criticisms and concerns about PrEP implementation include the following.

### *Data on the Effectiveness of PrEP, Especially in Women, Are Inconsistent*

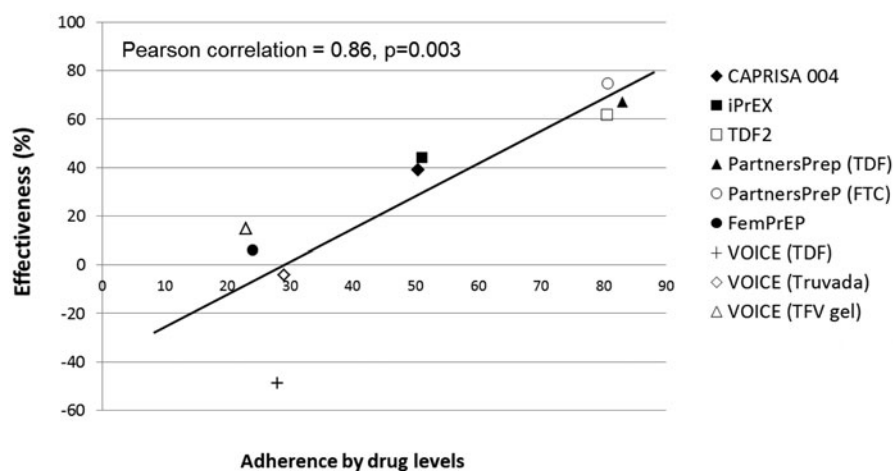
It is sometimes argued that the evidence that oral prophylaxis is effective in women is inconsistent. This is not true. The Partners PrEP and TDF2 studies have shown that daily ARVs can be taken with high adherence and thereby reduce the risk of HIV acquisition in women by up to 60 %. The lack of protective effect observed in the FEM-PrEP [21] and the VOICE trials [22] can partially be explained by suboptimal adherence. In the FEM-PrEP trial [23], only 24 % of the women allocated to the daily oral TDF/FTC group had detectable drug levels. Similarly, in the VOICE trial, only 23, 28, and 29 % of women allocated to the daily tenofovir gel, daily oral TDF and daily oral TDF/FTC groups, respectively, had detectable drug levels [22].

### *The Challenges of Long-Term Adherence*

Adherence is the Achilles' heel for PrEP and long-term, high adherence is essential for its success. The strong correlation between effectiveness and adherence is clearly evident when we compare levels of effectiveness observed in PrEP trials with an objective measure of adherence, i.e. the presence of drug (Fig. 2.2; Pearson correlation = 0.86;  $p = 0.003$ ). Poor adherence may lead not only to suboptimal protection but may also impact on drug resistance. This highlights the need for integration of behavioral interventions as integral to implementation of biomedical interventions.

Although clinical trials may achieve high adherence, the same may not pertain to “real-world” settings where PrEP may be implemented in underdeveloped public healthcare facilities without adequate attention to adherence support.

However, it is worth noting that drug adherence was also one of the key concerns raised when ART first became available as treatment. Concern about poor adherence was actually used as an argument against the implementation of these life-saving drugs in Africa. Experiences from implementing ART treatment has shown that high levels of adherence are achievable in a real-world setting, even in developing countries [24–26]. Although high adherence to treatment of HIV-positive people is encouraging, this may not be readily applicable to adherence in healthy asymptomatic people. On the other hand, adherence may not turn out to be an issue as the product's effectiveness may serve as strong motivation for adherence. Regardless, adherence is likely to be a challenge that will require a concerted effort to overcome and PrEP programs will need to include practical and proven adherence support programs.



**Fig. 2.2** Correlation between PrEP effectiveness trials and adherence as measured using detectable drug levels

### *Varying Adherence Leading to Varying Efficacy*

Both the CAPRISA 004 and iPrEX trials showed that effectiveness was closely linked to levels of adherence and presence of drug. In the CAPRISA 004 trial, the effectiveness of tenofovir gel increased to 54 % when women used the gel according to the dosing strategy in more than 80 % of all sexual encounters but was only 28 % when the gel was used less than 50 % of the time [6]. A case-control study of the iPrEX trial showed that effectiveness was increased to 90 % (95 % CI 71 %–98 %,  $p < 0.001$ ) in those with detectable drug [27]. Clearly, adherence and effectiveness are closely linked and it will be important to convey this message to potential PrEP users to ensure the highest possible adherence in the real world.

### *PrEP May Undermine Future AIDS Treatment by Causing Drug Resistance*

The risk of drug resistance from PrEP is markedly different from that observed when, for example, nevirapine is given to HIV-positive pregnant women, as those taking PrEP generally do not have circulating virus which can become drug-resistant. However, the possibility of resistance is present in instances where PrEP is taken for several weeks inadvertently by those with unidentified HIV infection; as was the case in the iPrEX trial where two men assigned to the TDF/FTC arm, whose HIV infection was not detected at enrolment, developed resistance to FTC [28].

A model based on the South African epidemic has shown that after 10 years of ART and PrEP rollout, the number of new infections would have decreased by 38 %

and the drug resistance prevalence would have increased to 11.4 %. This compares with levels of between 10 and 17 % observed in high-income countries. Importantly, most of the resistance is predicted to be a consequence of ART rather than from PrEP [29]. The main issue regarding resistance, however, is whether the use of PrEP will compromise an individual's ARV treatment options in several years' time when they may require ART. At present, there are no data to answer this question.

A separate concern about resistance is the use of the same drugs (e.g., Tenofovir) in therapy and prevention. Therapy failure is associated with the development of resistance and thereby the spread of resistant viruses, which in turn may compromise the efficacy of the same drugs (or occasionally, the same class of drugs) used for prophylaxis. Currently, there are over 30 licensed drugs to treat HIV, including several cost-effective non-tenofovir containing first-line regimens. Some consideration about setting aside a class (or classes) of ARVs for use in prevention only is warranted.

### ***PrEP Users May Reduce Their Use of Higher-Efficacy HIV Prevention Strategies Like Condoms***

The current oral and topical PrEP strategies are only partially effective, ranging from 39 to 73 %. Risk compensation is a potential concern when implementing any new suboptimal HIV prevention strategy [30] and is not specific to PrEP. Risk compensation could potentially undermine and even reverse the beneficial effects of PrEP, as shown by mathematical models on HIV epidemics in Botswana, Kenya, and southern India [31]. Although a low-efficacy intervention may be reversed by risk compensation, current evidence from medical male circumcision implementation has found this concern to be baseless. An assessment of the real-world effect of the rollout of medical male circumcision in a community in South Africa has shown no evidence of risk compensation after 3 years [18]. A more important consideration is that some of the PrEP strategies specifically empower women, who have no other alternative HIV protection strategies. Even a low-efficacy product would be critically important to large numbers of young women in South Africa who are unable to ensure their partner's fidelity or condom use. Indeed, PrEP is most appropriate for the target populations where condom use is low or nonexistent.

### ***ARVs Should Be Prioritized for AIDS Treatment***

Some have argued that it would be unethical to divert ARVs that would have been used for treatment for prevention [32], especially since only 54 % of those in need of ART were receiving it in 2011 [33]. Although it is a legitimate concern that eligible HIV-positive patients should be prioritized for ART for their own health and to save their lives, it is spurious to trade off treatment and prevention as if these drugs are being taken away from sick and dying patients to be given to healthy people.

Treatment and prevention strategies are a continuum in their use of ARVs—both are needed in conjunction with each other to ensure that ART provision is sustainable in the long term and to realize the quest to end the HIV epidemic.

One of the main reasons why so many people who are in need of treatment have not yet accessed it is because many do not know their HIV status. Based on ten recent national population-based surveys in sub-Saharan Africa, less than 40 % of people living with HIV know their HIV status [34]. In the 2008 South African National HIV survey, 74 % of those most at risk of acquiring HIV infection were unaware of their HIV status [35]. If self-denial, a common reason for not testing, is not overcome it will severely limit the potential impact of these new HIV prevention approaches [36]. Initiation of PrEP will require an assessment of HIV status and could therefore be used as an opportunity for not only scaling up PrEP to HIV-uninfected at-risk individuals but could also be used for identifying those who need ART for treatment.

### ***Is It Safe to Give ARV Drugs to Healthy Asymptomatic People?***

Tenofovir has an excellent safety profile and low rates of adverse effects. Less than 1 % of patients with HIV taking tenofovir in clinical trials had serious drug-related adverse events [37]. However, tenofovir may reduce bone density, exacerbate existing renal impairment, and has been associated with hepatic flares in chronic hepatitis B-infected individuals when the treatment is stopped [38]. Emtricitabine has a similar safety profile as tenofovir and adverse events occurring in clinical trials were generally of mild or moderate severity [39]. Although mild side effects are readily tolerated when medication is taken for therapeutic reasons, the same is not necessarily true when medication is taken by healthy asymptomatic individuals where even mild side effects may compromise adherence. Ongoing drug safety surveillance will need to be a component of plans for large-scale rollout of ARVs for PrEP. Hepatitis B testing and vaccinations for susceptible individuals at high risk may also need to be considered.

### ***Who Would Benefit Most and Criteria for Initiating and Terminating PrEP***

When resources are scarce, it is necessary to rationalize and prioritize certain high-risk groups for access to interventions over others. Determining who would benefit most will vary from country to country and although some groups, like MSMs and injection drug users (IDUs) are easily identifiable, identifying who should be prioritized in generalized epidemics is more complex. Nevertheless, before PrEP can be initiated, it will be important to establish the HIV status of the individuals and ongoing HIV testing would be an important component of any PrEP rollout program.

## **The Efficacy–Effectiveness Gap: Implications for Implementation Programs and the Implementation Science Agenda**

At present, there are no data available on the extent to which the outcomes achieved in the PrEP trials described earlier can be translated into real-world effectiveness. This leap from trials to implementation, generally referred to as the efficacy–effectiveness gap, can be substantial, as seen in implementation of prevention of mother-to-child transmission (PMTCT) programs. For example, a PMTCT program in Cote d’Ivoire showed that 40 % of HIV-positive pregnant women did not benefit from zidovudine to reduce mother-to-child transmission as only 60 % returned to the clinic for their HIV test results [40].

Some of the biggest contributors to the efficacy–effectiveness gap anticipated in the PrEP field will be willingness to know and monitor HIV status, suboptimal adherence levels, the extent to which people continue with the other proven prevention interventions (risk compensation), and the extent to which the existing public sector health services can facilitate uptake and maintain clients in long-term follow-up. The extent to which health services in countries most affected are sufficiently well managed to absorb the implementation of ARVs for prevention, in a manner that provides high uptake, adherence, and follow-up, will determine its success or failure. One approach to maximize the chance of success is to integrate PrEP as a component of existing comprehensive HIV prevention programs and services.

The implementation of PrEP faces substantial financial challenges. Besides the drug costs, the programmatic and laboratory monitoring costs, including HIV testing, hepatitis B virus testing, renal function assessment prior to tenofovir-containing PrEP initiation and then at regular intervals, of yet unknown duration, are likely to be substantial. Unfortunately, HIV prevention programs in regions with the highest HIV burden are already substantially underfunded and many highly effective prevention options such as condoms, are not being used at the scale and intensity needed [41]. A recent analysis shows that the per capita spending on health in high-HIV-burden countries like Kenya and Uganda is US\$ 17 and US\$ 16, respectively, with 60.7 and 50.2 % of the health expenditure being dedicated towards HIV [42]. The efficiency of health spending will need to be dramatically improved in these countries if PrEP is to be successfully implemented.

Although funds for Treatment for Prevention or PrEP may not be readily available at this point, it would be short-sighted to consider this in isolation. For PrEP, the long-term consequences of not implementing PrEP need to be considered, especially in women who may have no other effective options. Although the unmet need to provide antiretroviral treatment to all those in need is large, the opportunity to prevent new HIV infections cannot be passed over. Additional funding resources will need to be raised to implement PrEP as part of combination HIV prevention programs to avoid an unsustainable future with ever increasing numbers of people requiring life-long antiretroviral therapy.



## **Consequences of Not Implementing Biomedical HIV Prevention Interventions**

The challenges of implementing treatment for prevention or PrEP should not detract from the potential importance of these interventions. The realization of these strategies as part of an overall prevention plan is essential. The emphasis should be both on treating patients who require the ARVs for their own needs and also for those who need it for prevention. As was the case in MTCT, most of the concerns about scale-up can only be addressed in scale-up programs and not in relatively small phase I and II trials.

The regulatory approval of Truvada for PrEP by the FDA provides an opportunity to undertake scale-up programs but critically, these programs can be used as an opportunity to generate the evidence on how best to address the concerns and shortcomings of PrEP.

Initially, implementation programs should focus on providing PrEP to individuals at highest risk, e.g., MSM and young women in Africa and progressively scale up PrEP as part of a comprehensive HIV prevention package. To address the issue of the partial efficacy of PrEP, the impact of PrEP implementation should be monitored. Monitoring should include, at minimum, an assessment of HIV incidence rates, PrEP uptake levels, adherence levels, and the impact of PrEP uptake on condom use. Given the importance of adherence, programmatic implementation needs to carefully assess the factors impacting on adherence. In particular, the gender power imbalances and impact on power relations in acquiring HIV needs special attention. Resistance will also need to be closely monitored, both from use of Truvada as part of treatment and prevention. Long-term safety will need to be monitored, with special attention to kidney, bone mineral, and hepatitis B-related safety concerns. Implementation of PrEP will enable us to answer the questions about who to prioritize, when to initiate, and when to terminate by monitoring who benefits maximally and the period of highest risk that benefits most from PrEP.

Other clinical trial research should also continue in parallel, with some consideration being given to the assessment of different dosing strategies (daily vs. intermittent), as well as a range of formulations. Studies on alternative delivery mechanisms for PrEP such as gels and rings should also be pursued simultaneously.

## **Conclusion**

Treatment for prevention and PrEP have created newfound optimism in HIV prevention. ARVs increase options for HIV prevention, especially for specific high-risk populations such as young women in Africa. Despite the inherent challenges that lie ahead, implementation of ARVs for prevention is imperative and will be part of the solution to realizing the goal of finally turning the tide on the HIV epidemic.

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