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# Untangling the cost–effectiveness knot: who is oral antiretroviral HIV pre-exposure prophylaxis really for?

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Clinical trials of HIV pre-exposure prophylaxis (PrEP) antiretroviral drugs have shown excellent protection against HIV acquisition when plasma drug levels are detectable, indicating good adherence. Cost-effectiveness depends on epidemic context, adherence, drug cost, and other factors. For individuals at highest risk of HIV who are unable to use proven HIV prevention methods such as condoms and sterile injecting equipment, PrEP may be a workable option over short- to medium-term risky periods of their lives. Adding PrEP to HIV prevention programmes will be most effective as part of a combination prevention strategy that addresses both immediate risks and underlying vulnerabilities, and the pathways that link them. Determining who is most motivated to adhere to PrEP and supporting them through participant-centred approaches that assist people to find their own adherence solutions will be critical to determining the real-life cost–effectiveness of PrEP for HIV prevention and for whom HIV PrEP is most suited.

New HIV infections among adults and children worldwide were estimated by UNAIDS to be 2.3 million during 2012, an encouraging 33% reduction compared with 2001 [1]. Nevertheless, in the absence of a cure, every person who acquires HIV will eventually require antiretroviral therapy for the remainder of his or her life. Could antiretroviral drugs be used to prevent HIV acquisition in the first place? Who would be most suited for this HIV prevention tool? Would such pre-exposure prophylaxis (PrEP) be cost effective?

## Results of oral antiretroviral drug pre-exposure trials

Taking drugs to prevent an infection is not a novel concept. Travelers use malaria prophylaxis when visiting malaria-endemic areas. Antiretroviral drugs are used worldwide to prevent mother-to-child HIV transmission during pregnancy, labor and delivery and breastfeeding. A number of large biomedical HIV prevention trials conducted in populations as diverse as men and transgender women who have sex with men – the iPrEx trial [2], heterosexual serodiscordant couples – the Partners' PrEP trial [3], heterosexual men and women – the tenofovir disoproxil fumurate (TDF) 2 trial [4] and people who inject drugs – the Bangkok Tenofovir trial [5], have reported encouraging clinical trial results for oral PrEP since 2010. Effectiveness in reducing the risk of HIV acquisition using daily oral TDF/emtricitabine (TDF/FTC) ranged from a low of 44% in iPrEx [2] to a high of 75% in Partners' PrEP, which also found a 67% risk reduction for daily oral TDF alone versus placebo [3]. It deserves mention that all participants in these trials received a standard package of HIV prevention including condoms and HIV testing and counseling.

Two other trials testing oral TDF/FTC and/or TDF among women in sub-Saharan Africa found no effect [6,7]. A number of possible factors, such as differences in the trial populations, their sexual behaviors or concomitant conditions

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affecting genital mucosal integrity, could help explain these differences [8], but the most obvious explanation is adherence. Were trial participants taking the pills as instructed? In reality, only about 30% of women in the active drug arms of these trials had detectable plasma drug levels, revealing that the majority did not actually take their pills. In contrast, among people in the active drug arms of the trials with significant results, detectable plasma tenofovir diphosphate, the active form of TDF, was strongly correlated with relative risk reductions of 92% in iPrEx [2], 86% in the Partners' PrEP TDF arm and 90% in its TDF/FTC arm [3]. In the STRAND trial, directly observed dosing yielded TFV-DP concentrations that corresponded to an HIV-1 risk reduction of 76% for two doses per week, 96% for four doses per week, and 99% for seven doses per week [9]. Clearly while PrEP does not have a hope of preventing HIV if it is not used, it can provide excellent protection when it is.

## Who could benefit from oral antiretroviral PrEP?

This begs the question: who is PrEP for? Those who would benefit most are those at highest risk of HIV exposure, such as couples where one person is known to have HIV infection, men who have receptive anal sex without a condom with men of unknown HIV status, people who inject drugs with no access to or nonuse of sterile injecting equipment, sex workers and young women in high HIV prevalence settings, such as in southern Africa. Personal motivation and commitment to adhere are important determinants of whether PrEP could reduce individual risk of HIV infection. Interestingly, efficacy in the iPrEx trial was highest in those least likely to report condom use for receptive anal sex at baseline, suggesting that PrEP may be the first workable HIV prevention choice for some people [2].

At the program level, the addition of PrEP to the HIV prevention armamentarium will be most effective as part of a combination prevention strategy that addresses both immediate risks and underlying vulnerabilities and the pathways that link them. This means stigma reduction and changes in sexual norms along with risk reduction counseling and promotion and provision of condoms for those exposed sexually. It means offering opioid substitution therapy and providing ready access to sterile-injecting equipment for those exposed through injecting with contaminated needles and syringes. On the individual level, people who are unable to use these conventional HIV prevention tools when they are offered may find that PrEP works better for them. On the program level, PrEP cannot substitute for any of the basic HIV prevention strategies but it could be added to them. However, will it be a cost-effective addition?

## Cost–effectiveness studies of oral antiretroviral PrEP for HIV prevention

A number of studies have assessed the cost–effectiveness of oral antiretroviral PrEP, reporting results as the cost per infection averted, cost per life-year saved, cost per quality-adjusted life-year gained, cost per disability-adjusted life-year averted and years on PrEP per infection averted. A recent systematic review of 13 of these cost–effectiveness modeling studies explored the cost and impact of scaling up PrEP for HIV prevention [10]. The studies had modeled PrEP introduction in populations such as heterosexual couples, men who have sex with men and people who inject drugs, in settings as diverse as southern Africa, Ukraine, USA and Peru. Assumptions about cost, epidemic context, program coverage levels, prioritization strategies and individual-level adherence influenced the extent of the potential impact of PrEP. All of these are considerations that country policy makers and program planners need to address from the local perspective in assessing whether PrEP would be a cost-effective addition to their national HIV prevention program.

The review concluded that the most cost-effective strategy appeared to be delivery of PrEP to key populations at highest risk of HIV exposure, that is, where HIV incidence is highest. However, when the current price of drugs is high, as in Peru, PrEP may not be affordable even if it could have a substantial impact among men who have sex with men. Furthermore, offering PrEP to marginalized and stigmatized populations would require effective outreach strategies, the costs of which were not represented in most analyses. In settings such as the Ukraine, PrEP for people who inject drugs could play a role if it was added to significantly expanded antiretroviral treatment (ART) and opioid substitution therapy coverage.

In southern Africa, oral PrEP may be cost-effective to prevent heterosexual HIV acquisition, but it raises questions about opportunity costs, social justice and equity. Debate about the tradeoffs for antiretroviral drug use for HIV treatment versus HIV prevention is intense [11]. Should the rule of rescue [12], which gives weight to rescuing people whose lives are imminently threatened even if fewer lives are saved overall, take precedence over utilitarian approaches that favor using resources most efficiently to prevent disease and save the most lives [13]?

These ethical debates are taking place against a backdrop of evolving science. A ground-breaking trial found that early ART for the HIV-positive person in a serodiscordant couple reduced the risk of genetically linked HIV transmission to the HIV-negative person by a striking 96% [14]. A recently published cost–effectiveness study of early treatment for prevention in HIV serodiscordant couples found this strategy in India to be cost effective over 5 years and very cost effective over a lifetime, while in South Africa, it was cost-saving over 5 years and very cost-effective over a lifetime [15]. However, it remains unclear whether early treatment would reduce or improve quality of life and would result in better or worse retention and adherence. The Strategic Timing of Antiretroviral Therapy trial [16] underway in 35 countries, has completed enrolment of 4000 people with CD4 counts above 500 cells/μl [17], the ART initiation threshold recommended now by the WHO [18]. It should provide the definitive answer as to whether early treatment has individual clinical benefits. As with PrEP, access and adherence are key determinants of ART effectiveness. ART at any CD4 count level can only achieve the undetectable viral loads that are associated with clinical effectiveness and reduced

HIV transmission risk if people living with HIV can access it and adhere well.

## Beyond ethics & cost–effectiveness: other considerations for decision-makers

Theoretical cost–effectiveness can help orient decision makers with respect to whether the introduction of PrEP would be a good idea in general in their setting [19]. The price of the drugs used in current PrEP formulations varies around the world depending on negotiated ART agreements. It is likely that a change in indication to include PrEP would not influence price as the anticipated increase in demand would not be large. As for regulatory approval, in July 2012, the US FDA, based on the iPrEX and Partners' PrEP results, approved daily TDF/FTC to be used in combination with safer sex practices for the reduction of risk of sexually acquired HIV among adults at high risk of HIV exposure [20]. To date, no other regulatory body has ruled on PrEP.

However, at the very heart of the issue is the question of whether promising clinical trial results for antiretroviral PrEP can be translated into effective real-life programs. WHO has published guidance on the use of oral PrEP in the context of demonstration projects for serodiscordant couples and for men and transgender women who have sex with men at high risk of HIV infection [21]. These projects aim to address perplexing implementation questions such as how to ensure HIV-negative status before initiating PrEP; what HIV testing frequency is ideal; how safe is TDF/FTC over the longer term; what are the best service delivery options for initiation, follow-up and resupply of drug; how much might PrEP add to antiretroviral drug resistance; and how best to foster and support high levels of adherence.

Finally, while all these questions are being answered, there still remains arguably the most important consideration influencing whether oral antiretroviral PrEP will be a cost-effective addition to HIV prevention programs: will those for whom this could be a beneficial addition to their HIV prevention choices really want to take it? Will their concerns about their high risk of acquiring HIV outweigh any short-lived side effects and possible stigma related to taking antiretroviral drugs? Will PrEP provide a desirable prevention option for those unable to negotiate condom use or to access and use sterile injecting equipment? Could it be an entry point attracting people to services that can assist them in also considering other risk reduction strategies? PrEP may be an appropriate short- to medium-term strategy for individuals experiencing specific high-risk periods in their lives. However, achieving adequate drug levels at the site and time of potential HIV exposure relies on self-directed pill taking. The challenge for providers is how best to assist people to decide whether oral PrEP will be a good choice for them, given their sexual and/or injecting practices and the prevention measures they are able to implement in the current context of their lives.

We can create contexts that foster healthy choices and provide people with an array of different prevention options and tools for different situations and times of their lives, but they must be empowered to act on the choices that they have made [22]. Determining who is most motivated to adhere to PrEP and supporting them through participant-centered approaches that assist people to find their own adherence solutions [23] will be critical to determine the real-life cost–effectiveness of PrEP for HIV prevention and for whom HIV PrEP is most suited.

### Financial & competing interest disclosure

*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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