HIV/AIDS

ARVs as HIV Prevention: A Tough Road to Wide Impact

Antiretrovirals face formidable obstacles for wide-scale prevention of HIV infection.

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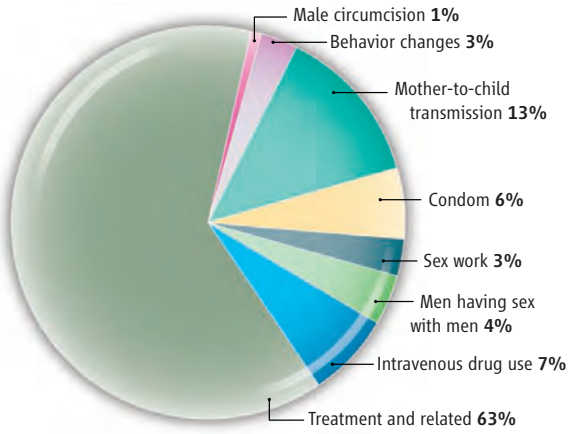
Compelling new evidence showing that oral antiretroviral drugs (ARVs) can prevent heterosexual HIV transmission has recently burst upon us. The HPTN 052 randomized study confirmed earlier observational data that, if the HIV-positive partner in a discordant couple took ARVs, transmission to the HIV-negative partner was virtually eliminated, at least for more than 2 years (*1*). Two randomized studies found that taking ARVs by the HIV-negative partner in a discordant couple (preexposure prophylaxis or PrEP) also reduced transmission substantially (*2*). These results have ignited enthusiasm for ARVs as a breakthrough for HIV prevention. Indeed, Joint United Nations Programme on HIV/AIDS (UNAIDS) Executive Director Michel Sidebe has described it as "game changing" (*3*).

Are ARVs a magic bullet to stop the global epidemic in its tracks? It is not that simple. First, two additional trials of oral PrEP failed to show an impact (*4*). Moreover, such trials are conducted under optimal conditions designed both to maximize proper use of ARVs and to reduce risky behavior. Achieving an impact of ARVs at the population level is quite another matter. HIV is an elusive enemy, and a variety of major logistical, cost, biologic, and behavior impediments stand in the way of broad impact at scale.

Identifying infected and uninfected at high risk. There are an estimated 34 million infected people globally of whom some 6.6 million are already taking ARVs. But 2.7 million become infected each year (*5*). Simply identifying and reaching a major proportion of the infected but untreated (and frequently unaware) people is a Herculean task. Many people are difficult to reach and/or resistant to testing. For example, Lesotho, a relatively advanced compact country with the world's third highest HIV prevalence, launched a national campaign in 2004 to test everyone. Yet by 2009, only just over half of the adult population had been tested even once (*6*). And the perpetual stream of newly infected people increases the testing burden. Even an exceptionally optimistic model (that assumed universal testing every year, nearly complete adherence, and 40% of impact from other prevention programming) projected it would take a decade to bring new infections in generalized epidemics (where the epidemic affects a substantial portion of the general population) close to zero and 50 years for virtual infection elimination (*7*).



Global HIV program funding 2011 [Derived from (*19*)]. Costs do not include general support and research.

For oral PrEP, the reservoir of uninfected people is far too large. Rather, the challenge is identifying those potentially at substantial risk for HIV acquisition. For some, that may be relatively straightforward, such as identified negative partners in a discordant couple, but beyond those the potential for PrEP is unclear—even for some at higher risk, such as those with multiple sexual partners.

Missing very early infections. Within the first weeks of infection, people are much more contagious than in the multiyear chronic phase, because of both the higher viremia and the nature of early transmitted virus (*8*). This early infectiousness allows for chains and clusters of rapid transmissions crucial to propagation of the epidemic (*9*). Such infections account for very roughly one-third of transmission events in generalized epidemics, depending on the maturity of the epidemic, but they can propagate rapidly and spawn subsequent generations of onward transmissions. But most current HIV tests do not detect acute infections (*8*). Even with more sensitive tests, the interval of maximal infectiousness is so narrow, and HIV incidence so relatively low, that few people are tested during this critical time.

Acceptance and long-term adherence. For ARVs as prevention to have a substantial impact, very large numbers of those persons testing positive—most symptom-free—would need to take them voluntarily and consistently for a lifetime. Even now, adherence is far from perfect, and some patients discontinue for a variety of reasons, including drug side effects (*10*). Adherence among symptom-free people is even more problematic, especially if they experience side effects.

These issues are greater for an HIV-uninfected person, who might choose PrEP, as ARVs have no clinical benefit. Poor adherence was apparently a major reason for failure to show impact in two recent oral PrEP trials (*4*), although low levels of ARV in the female genital tract after oral administration may have also limited efficacy (*11*).

Drug resistance. ARV-resistance mutations already are found in untreated patients. Providing ARVs on a more massive scale for many years opens the door to more resistance, especially when use would be long and adherence possibly lower. Evidence from Africa indicates the proportion of ARV recipients with resistance mutations has increased each year since ARV roll-out (*12*). Resistance has been observed with PrEP apparently early during infection (*13*).

Risk compensation. The concept that belief in the protective powers of ARVs could lead to more risky behavior is a major concern. Promotion of condoms in a community intervention in Uganda resulted in increased risky behavior compared with that of the control population (*14*). Riskier sexual behavior has increased in the large Amsterdam cohort of men who have sex with men (MSM) from 1996 onward (*15*). Evidence from a Swiss cohort indicates increased risky sex among those taking ARVs who are informed of

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ARVs' prevention benefit (*16*). These findings argue for not relying only on ARVs but also reinforcing complementary behavioral risk reduction, as occurred in each successful clinical trial. For PrEP, a particular worry is that some individuals would take ARVs sporadically and then engage in risky sex.

Drug toxicity. For those with advanced HIV, the benefit of ARVs far outweighs the risks, and HPTN 052 found some clinical benefit to individuals in earlier stages. Still, ARVs have toxicity that becomes an even more important concern for those who are HIV-negative. For example, tenofovir, an ARV included in all prevention trials to date, may cause kidney injury (*17*). Further, nucleoside reverse transcription inhibitors induce accelerated mitochondrial DNA mutations that might result in premature aging and eventual multiorgan disease (*18*).

Cost and human resources. Even with massive funding, many programs are challenged to meet current ongoing costs for treatment. Recent global estimates indicate nearly two-thirds of the $7.0 billion current basic program funding supports treatment- and care-related services (see the chart, page 1645) (*19*), even though less than half of treatment-eligible people are receiving ARVs. In a world currently beset with economic stress and with increasing emphasis on other compelling global health priorities, the prospect of increasing provision of ARVs severalfold seems unrealistic. Furthermore, the cost would be cumulative, as survival improves and progressively more people take ARVs for treatment and prevention. Although some economies of scale could accrue, identifying HIV-infected people who are the most difficult to find would likely increase marginal costs and further stress frail health systems.

Concentrated epidemics. Although generalized HIV epidemics represent most of the global burden, ARVs also have potential for situations where HIV largely affects MSM and to a lesser degree injecting drug users (IDUs). This is the case in the United States, where infection rates are lower and resources are much greater. About four-fifths of those living with HIV in the United States have had at least one HIV test (*20*), but service delivery to these populations can be difficult. Missing acute infection is definitely a problem; some viral genetic-linkage evidence from Canada suggests a substantial proportion of transmission among MSM may result from serial acute infections (*21*). A study of PrEP in MSM in the United States and South America found an efficacy of only 44%, at least partly attributable to poor adherence (*22*). The ability to identify HIV-positive people, link them to care, and achieve durable viral suppression has been difficult in the United States (*23*). Financing is also a problem in providing ARV assistance for U.S. low-income patients who meet current treatment guidelines (*24*).

Some reports have suggested an impact of ongoing ARV treatment programs on reducing incidence of HIV in urban populations, e.g., MSM in San Francisco (*25*) and IDUs in British Columbia (*26*). However, these are imprecise observational analyses that follow new diagnoses rather than true incidence and are subject to important confounders (*27*). Conversely, HIV diagnosis has increased in settings of MSM in Canada and Australia (*28*) and incidence in an intensive cohort in Amsterdam (*15*), despite widespread ARVs. HIV incidence in the United States has remained constant since the introduction of ARVs (*29*).

Conclusion. Oral ARVs definitely have a supporting role to play in prevention as part of a combination approach based on every tool we can muster. Such tools include male circumcision, condoms, partner limitation, behavior change, and needle exchange working in synergy (*19*). But we need to proceed selectively and incrementally and to gather more evidence. Priority for treatment should be given to those with advanced disease who are as yet untreated. They would benefit clinically and provide greater prevention impact because their lower CD4 counts and higher viral load make them substantially more likely to transmit infection (*30*). Some modeling suggests high levels of ARV coverage in a few key countries may be reducing transmission (*5*). Other priorities include individuals more likely to transmit HIV, such as sex workers, and a partner in an identified discordant couple regardless of CD4 count. Women identified during pregnancy who successfully take ARVs to prevent vertical transmission could also be a priority. These priorities align with a recent President's Emergency Plan for AIDS Relief (PEPFAR) advisory (*31*). At the same time, we need to strengthen behavioral risk reduction and adherence for these high-priority individuals to avoid compromising ARV's prevention benefit.

We do not know the extent to which findings in small-scale trials will extend to large-scale implementation. Some 50 studies on ARVs as prevention are under discussion (*32*), of which at least four are in larger study populations. Such research should inform any major expansion of ARVs as prevention. We also need better, cheaper, longer-acting, more user-friendly, and program-friendly ARVs for treatment and prevention.

Primary prevention suffers from striking underfunding (see the chart), especially the core prevention approaches—behavior change, male circumcision, and condoms. Nevertheless, current prevention interventions are beginning to take hold. HIV incidence is declining globally (*5*) albeit slowly. Remarkable declines in incidence related to reduced risky behavior have occurred in key African countries (*33*). Accordingly, ARVs as prevention must not jeopardize already precariously low funding for complementary prevention interventions, particularly the behavioral ones. Likewise, research to develop HIV vaccines must remain a priority. ARVs are no "magic bullet." But ARVs' best potential is to contribute to the existing combination arsenal, which, well applied, can have a major impact in stemming the global HIV pandemic.

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