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Turning the Tide Against HIV

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Although the annual number of new HIV infections (incidence) declined from a peak of 3.5 million in 1996 to 2.6 million in 2009, the total number living with HIV continues to rise as more people live longer. While 6.6 million people with HIV are now on antiretroviral treatment (ART), 9 million are waiting to receive it, with two people newly infected for every person starting ART (3). Twenty million more people are predicted to acquire HIV by 2031, which will increase treatment costs up to $35 billion a year (2). This raises issues of sustainability. Thus, reducing HIV incidence is critical to keeping alive the promise of universal access to HIV prevention, treatment, care, and support.

New biomedical tools with proven effectiveness should be added to individual-level behavioral and population-level structural components, with national policies guided by cost-effectiveness and population impact assessed in randomized controlled trials (RCTs). Sequential implementation of each new biomedical intervention is an inevitable process for unlicensed products. However, we recommend accelerated assessment of potentially beneficial combinations through innovative RCTs that assess more than one biomedical tool against a common control.

RCT Evidence of Success

Combinations of behavioral and structural intervention strategies to reduce vulnerability and risk of HIV infection have been applied for nearly three decades with differing success (3). However, a number of new biomedical tools have demonstrated success in RCTs: medical male circumcision (MMC); daily oral tenofovir (TDF) plus emtricitabine (FTC) used as preexposure prophylaxis (oral PrEP) by HIV-negative men who have sex with men (MSM); 1% tenofovir gel (microbicide) applied vaginally before and after sex with HIV-infected individuals receiving ART; and, most recently, immediate ART for the HIV-positive partner to prevent onward sexual transmission (4–7) (see the chart).

In contrast, daily oral TDF/FTC used as PrEP by heterosexual women did not appear to provide benefit in the FEM-PrEP trial that is closing early after a planned interim review revealed equal numbers of HIV infections in the active and placebo groups (4). Independent pharmacokinetic studies of oral dosing suggest that TDF drug levels are 10 to 100 times lower in vaginal versus rectal tissues (9). This might provide one explanation for the difference in efficacy of oral TDF/FTC against vaginal (women) and rectal (MSM) HIV transmission.

Recent findings indicate that early use of ART [treatment for prevention (T4P)] by an HIV-infected individual reduced heterosexual transmission to an uninfected partner by 96% when couples also received free condoms, safer-sex counseling, and treatment for sexually transmitted infections (HPTN052) (10). This strengthens previous evidence from a meta-analysis of ART estimating a 92% reduction in transmission (11). Although early ART for serodiscordant couples (where one partner is infected) may be feasible in many settings, offering immediate T4P to all who test HIV-positive is challenging in settings where barely 50% of those medically eligible (based on decline in CD4 T cell count) are receiving ART.

New Approaches to Trial Design

Specific approaches would include focused assessment of MMC combined with microbicide gels for men’s female partners. A second combination to evaluate would be T4P with antiretroviral (ARV) PrEP (microbicide for women, oral for MSM) for the HIV-negative partner. At least 7 of the 39 (18%) sexual transmissions in the HPTN052 trial involved virus that was genetically distinct from that of the primary infected partner and were thus presumably acquired from other partners outside the primary relationship (10). Thus, the offer of ARV PrEP for the HIV-negative partner would likely add benefit to treating the positive partner in serodiscordant couples, would facilitate safer conception (12), and may provide a more cost-effective option per infection averted than early ART alone.

It is, however, widely accepted that a fully efficacious vaccine providing durable (years) protection against HIV would have the biggest impact on HIV incidence. Nevertheless, mounting a protective immune response within hours of exposure is a biological challenge, particularly if viral exposure is high. Positive interactions could be explored by assessing the impact of combining vaccines with other biomedical interventions.

It is plausible that concomitant PrEP might prevent HIV acquisition during the course of immunizations before the full development of vaccine-induced immunity. A second potential positive impact would be seen if combining PrEP and vaccines had additive or synergistic interactions once the course of immunizations were complete. Current understanding is that HIV infection is mostly initiated by a single viral variant that requires local amplification in mucosal tissue before disseminated systemic infection is established (13). When viral exposure is extremely high, as is the case in acute infection, multiple variants capable of establishing many foci of infection may be transmitted. Here, more than one biomedical technology is likely needed to prevent HIV acquisition.

Lessons might be learned from the Thai RV144 vaccine trial, based on a canarypox vector prime (ALVAC)–protein boost, that demonstrated partial protective efficacy in cohorts at low risk of HIV exposure (6). Investigations are under way to try to define the correlates of protection in this trial. It is unclear whether those infected had suboptimal immune responses relative to those protected or if they were exposed to a higher and/or more frequent infectious challenge that was sufficient to overcome the vaccine-induced immunity. If the latter, it is certainly plausible that the implementation of T4P microbicides, oral PrEP, and/or MMC could reduce both the infectiousness and frequency of viral exposure in a given population, providing conditions that might significantly increase vaccine efficacy. This hypothesis could be explored in the design of the proposed ALVAC-protein prime-boost trials based on the RV144 results currently being discussed in Thailand and South Africa.

Another unexplored possibility is that vaccinated subjects protected from infec-
by also using ARV-PrEP might display boosted vaccine-induced immune responses (the virus working like a booster vaccine) each time they are exposed to HIV. This might focus vaccine-induced immune responses to better recognize virus from their infected partner(s). Indeed, evidence from nonhuman primate (NHP) studies indicates that animals exposed to infectious virus when protected by PrEP demonstrate cellular immune responses to the challenge virus (14, 15). Such immune responses in these nonvaccinated animals were insufficient to protect animals from subsequent challenge in the absence of PrEP (15). Studies are now needed to determine whether ARV-protected exposure to infectious virus in vaccinated animals can influence immune responses sufficiently to increase vaccine efficacy.

Dual-delivery technology for concomitant administration of vaccine candidates and vaginal ARV-microbicides is also under development. The simplest approach is the co-formulation of HIV vaccines in a microparticle carrier gel that might be amenable to repeatedly boosting vaginal immune responses, while at the same time delivering topical ARV protection against vaginal HIV acquisition. More sophisticated approaches have been the development of intravaginal ring (IVR) technology that could provide both sustained release of preventive ARV-drug dosing (months) and pulsed exposure of a vaccine (hours to days) (16). Given that IVRs are capable of delivering ARV dosing for up to 3 months, incorporating a pulsed vaccine dose in each ARV-containing IVR could provide regular boosting of vaginal immunity. Another possibility is the combination of vaccine candidates and long-acting (months) injectable PrEP formulations such as the rilpivirine (TMC278) injectable nanosuspension (17). Here, both vaccine and injectable PrEP could be delivered in a similar fashion to injectable contraception, which would remove the issue of adherence (remembering to take the drug).

However, combinations may also have negative implications. The most important of these is the possibility that individuals who are using condoms consistently may stop doing so in favor of a partially effective technology. Open-label trials (where participants know what they are using) with biological outcomes (HIV acquisition) are the best way to assess concerns about risk compensation (adjusting behavior based on perceived protection) while learning about implementation. Biomedical combinations may have other negative implications; for example, using the same ARV drugs for treatment and prophylaxis may exacerbate circulating drug resistance if efficacy is only partial. These are complex issues, mandating timely communication about the rationale, design, and results of combination approaches.

Currently, most human clinical trials remain focused on determining safety and efficacy of individual biomedical interventions. Although this remains a priority, we recommend a broadening of focus to accelerate rigorous evaluation of combination approaches. This means a move away from single biomedical interventions to an emphasis on combinations that provide the greatest impact on HIV incidence in diverse epidemic scenarios. A coordinated approach tracked by normative bodies like Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization is required to advance prevention science efficiently by designing and conducting RCTs to assess the added value of single biomedical interventions or combination strategies (18). In addition, expansion of preclinical studies is needed to assess the biological plausibility of additive or synergistic interactions between ARV prophylaxis and vaccines to create lower-risk conditions that might make partially efficacious vaccines a viable option.

We predict that combining implementation of new biomedical prevention tools to create additive or synergistic effects will stimulate incremental reductions in HIV incidence. This, in turn, will raise the bar of evidence required for evaluation of new approaches, as reduced incidence will necessitate larger, and therefore more costly, trials and place an intrinsic research value on higher-incidence cohorts. For PrEP, this will mean increasing emphasis on surrogate markers of activity, including pharmacokinetics and pharmacodynamics, to demonstrate potential superiority over approaches with proven efficacy in RCTs. For vaccines, it will require proof of efficacy in NHP studies, definition of correlates of immune protection, and demonstration of their induction in early phase I/II clinical trials.

Study of the interactions among, and combinations of, novel HIV biomedical intervention tools represents the next imperative for HIV prevention science—offering hope, at last, for a tangible impact on halting and reversing the HIV pandemic.

References