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Antiretrovirals for HIV Prevention: New Steps Forward and New Questions

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For more than a decade, clinical researchers have established the foundations for believing that antiretroviral treatment for HIV-infected individuals made them less infectious, and that prophylactic use of the same drugs could protect exposed, uninfected persons. In the summer of 2010, high-risk South African women who applied a topical vaginal gel peri-coitally in the CAPRISA 004 trial had a 39% decrease in HIV incidence compared to those who used a placebo gel (1). This important observation was soon followed by the iPrEX Study which enrolled at-risk men who have sex with men (MSM) in 6 countries, finding a 44% decrease in HIV incidence in those randomized to take a co-formulated dose of tenofovir-emtricitabine daily compared to a placebo (2). Both studies also demonstrated the Achilles' heel of chemoprevention, that protection was highly correlated with medication adherence; and in both studies non-adherence was common (1, 2).

Another approach to using antiretrovirals for prevention was validated by the HPTN 052 trial results announced this past summer, which demonstrated that HIV-infected individuals in serodiscordant relationships who initiated antiretroviral therapy at higher CD4 counts (i.e. between 350-550 cells/milimeter^3), were 96% less likely to transmit HIV to their partners (3). The HPTN 052 findings also focused the question how antiretrovirals should be most strategically used to arrest the epidemic. Would it be best to only expand treatment for infected individuals at CD4 levels higher than most national guidelines, or could the adjunctive, selective use of chemoprophylaxis for individuals at highest risk to acquire HIV infection augment prevention efforts? Some modeling studies have supported the idea that expanded treatment and selective chemoprophylaxis for high risk populations (e.g. MSM,

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sex workers) could more rapidly curtail the epidemic than either approach alone (4, 5), but the large unmet treatment needs of people living with advanced HIV suggest that expanded access to medication remains a priority.

Additional questions about the benefits of primary chemoprophylaxis have emerged in the past few months, as protective benefits were not consistently noted in subsequent trials. In the FEM-PrEP Study, in which at-risk southern African women were randomized to use oral Tenofovir-Emtricitabine or placebo, the study was discontinued early because of lack of efficacy (6). However, in two subsequent trials, the Partners PrEP Study (7) and the Centers for Disease Control Botswana TDF-2 Study (8), antiretroviral chemoprophylaxis was found to be effective in decreasing HIV transmission among at-risk African heterosexual men and women. More recently, the VOICE Trial discontinued two of its active arms, oral Tenofovir-Emtricitabine and topical tenofovir gel (9). It is not yet understood why there were differences between this study and several other trials that enrolled at-risk women, which showed that oral or topical chemoprophylaxis was protective. Some of the reasons for the discrepant results could include the relatively lower cervicovaginal concentrations of orally administered tenofovir compared to mucosal levels achieved after topical gel application (10), differing patterns of adherence in some populations, and the attenuation of chemoprophylactic benefit when concomitant sexually transmitted infections or other causes of genital tract inflammation are present. Studies are underway to address the contribution of these different possibilities to the range of results noted in recent trials. Enhanced understanding of how much drug exposure will provide adequate protection is needed (11), in conjunction with improved assessments of, and interventions to promote, medication adherence.

So where does this leave the field? There are several other chemoprophylaxis studies under way to try to tease out the reasons for the inconsistent findings in these recent trials. The FACTS 01 trial in South Africa is evaluating pericoital Tenofovir vaginal gel in high risk women, similar to the CAPRISA 004 regimen, and may help determine the relative efficacy of this approach, by either corroborating CAPRISA 004, or the disappointing VOICE gel results (12). There are also other studies enrolling at-risk women in oral chemoprophylatic studies, including the continuing oral Tenofovir-Emtricitabine arm of VOICE. But for the time being, the focus in HIV chemoprevention needs to be on expanding treatment options for HIV-infected women and men in areas where the epidemic is expanding most rapidly. While increasing the census of people on treatment may seem straightforward, it involves a series of structural interventions that have not been fully scaled-up in the developing world, or even in the United States. The full roll out of “treatment as prevention” includes optimizing routine HIV testing for all inhabitants of communities where HIV is prevalent, and repeated testing for individuals who have some level of new risk after testing negative initially. Once individuals are newly identified as infected, they need to be engaged in care, and once they establish contact with a provider or care team, they need to be encouraged to initiate antiretroviral therapy, and given support to adhere to their regimen and decrease behaviors that might transmit HIV to others.

Relying on treatment alone to stop the AIDS epidemic is a worthwhile goal, but residual challenges exist, since in many parts of the world the scaling-up of testing, linkage to care, providing stable access to medications and maintaining adherence remain daunting tasks. The recent announcement by the Obama Administration to expand treatment for 2 million additional people living with HIV (13) helps address a great unmet need, but sadly will still leave the majority of people living with HIV untreated. Thus, barring a major infusion of resources from other donors, the ability of “test and treat” to stop the epidemic immediately is limited, though over the longer term, it will ultimately prevent millions of new infections. In the meantime, there are some sub-populations who may particularly benefit from

chemoprophylaxis, such as men who have sex with men, injection drugs users, and sex workers. Thus, a nuanced approach that addresses the judicious use of antiretrovirals for prevention in diverse specific settings is needed.

Despite the lack of efficacy seen in some recent primary prevention trials, the positive findings seen in others suggests that chemoprophylaxis is a viable strategy for some at risk populations, that can, and should, be optimized. The future success of antiretrovirals for prevention may entail the development of new combinations that are particularly active at genital and rectal mucosal sites, and development of formulations that are longer acting and, thus, not dependent on daily or pericoital adherence. Studies are also underway evaluating new antiretrovirals that may have particularly favorable mucosal chemoprotection features. Very similar to another public health challenge, the prevention of unwanted pregnancy, the development of chemoprophylaxis will require a thorough understanding of community norms, and the acceptability of different approaches.

The use of antiretrovirals for primary and secondary HIV prevention remains a promising approach, which should have a major impact in slowing-down the spread of the epidemic globally. Coupled with expanding HIV testing, treatment and care, selective use of chemoprophylaxis in conjunction with other evidence-based prevention approaches, such as male circumcision and harm reduction for injection drug users, may create the “tipping point” in which the current level of more than 2.5 million HIV infections annually can finally be substantially curtailed (14). The past few years have provided glimmers of hope, while reminding clinical researchers that the accrual of knowledge and the implementation of best practices are incremental processes, requiring curiosity, humility, tenacity, and political will.

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