EDITORIAL

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Integrating HIV Prevention Into Practice

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At the beginning of the human immunodeficiency virus (HIV) epidemic 30 years ago, the main methods for prevention were clean needles and condoms. Even though these available methods would work, their success was completely dependent on human behavior. However, over the past decade, biomedical prevention of HIV has come of age, in the wake of the extraordinary success of antiretroviral therapy (ART) for treatment of the HIV-infected person. In quick succession, effective approaches for prevention were developed and implemented, including prevention of mother-to-child HIV transmission through birth and breastfeeding, medical male circumcision, preexposure prophylaxis (PrEP), vaginal microbicides, and prevention of transmission to uninfected partners of an HIV-infected person with effective ART.

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In recognition of the increasing convergence of behavioral and biomedical interventions toward a combined HIV prevention approach, an expert panel convened by the International Antiviral Society-USA (IAS-USA) presents recommendations[1] in this issue of *JAMA*. Although other international (World Health Organization[2]) and domestic agencies (US Department of Health and Human Services[3,4]) have issued important guidelines, the 2014 recommendations from the IAS-USA panel bring into sharp focus the role of clinical settings in HIV prevention. These recommendations[1] highlight the opportunity to capitalize on the prevention effects of established biomedical approaches, reinforce the importance of behavioral approaches, and describe how these approaches might be better integrated into clinical care settings, expanding the reach and potential benefit of these interventions.

The opportunity to make use of treatment as a prevention strategy has been met by both optimism and caution from different sectors of the HIV community, an indication of the complex issues this proposition raises. Achieving viral suppression through ART has benefits for an individual living with HIV, his or her partner, and the broader community in which he or she lives. Reducing HIV transmission has the potential to slow the epidemic, but requires early detection of new infections through increased testing and high levels of treatment uptake and adherence. The strong ethical case exists that the decision on when to commence treatment must be based on the benefits and risks to the individual, rather than any potential public health gains, however significant they might be. Increasing evidence suggests achieving such public health benefits through early initiation of ART might not conflict with an individual's own health and welfare, even if his or her CD4 cell count remains high (>500/μL) given that: viral suppression may protect against the development of non-AIDS-defining conditions; newer ART regimens are associated with low risk of adverse events; and the psychological benefit of knowing the risk of transmitting HIV to a person's partner is reduced.[4] Findings from the Strategic Timing of Antiretroviral Treatment (START) trial (clinicaltrials.gov identifier: NCT00867048), expected in 2016, should help resolve any remaining uncertainty around the benefits and risks of starting treatment early (with a CD4 cell count >500/μL) compared with deferred treatment initiation (when CD4 cell count <350/μL).[5]

In another article in this issue of *JAMA*, Mugo and colleagues[6] report important follow-up data on pregnancy outcomes from the Partners PrEP Study for the prevention of HIV infection in serodiscordant heterosexual couples in Africa. The previous report from this study[7] demonstrated efficacy of tenofovir disoproxil fumarate with or without emtricitabine in reducing HIV incidence with key safety outcomes no different from placebo. Following the unblinding of the trial in 2011, study participants who received placebo were rerandomized to emtricitabine/tenofovir or tenofovir alone, and were then followed up for an additional 12 months and beyond for pregnancy outcomes.

Mugo et al[6] report in this valuable, more detailed analysis of pregnancy outcomes from the study that among 1785 HIV serodiscordant heterosexual couples in which the female partner was not infected with HIV, a total of 431 pregnancies occurred, with no significant difference in pregnancy incidence among women assigned to receive placebo, tenofovir, or emtricitabine/tenofovir. In addition, there were no statistically significant differences among treatment groups in the rates of pregnancy loss, preterm birth, or congenital anomalies. However, it appears (from the magnitude and asymmetry of the confidence intervals) that there may be a signal suggesting potential harm as pregnancy loss based on the emtricitabine/tenofovir vs placebo comparison (absolute difference ending in pregnancy loss of 10.2%; 95% CI, −5.3% to 25.7%) and on the post hoc emtricitabine/tenofovir vs tenofovir alone comparison (absolute difference ending in pregnancy loss of 9.2%; 95% CI, −1.7% to 20.1%).

These intriguing findings reported by Mugo et al[6] provide important information from one of the largest studies of exposure to these nucleoside analogues in HIV-negative persons and therefore must be considered carefully. Tenofovir and emtricitabine are both category B drugs, but this signal suggesting a possible association with pregnancy loss has not to date appeared in studies of HIV-infected persons, suggesting that this observation deserves evaluation in future studies. Moreover, the nucleosides were stopped according to the trial protocol no later than 6 weeks into the pregnancy, albeit this period is highly sensitive to subsequent adverse pregnancy outcomes, but exposure to these drugs may be longer in the real-world setting.

Other safety signals from the use of tenofovir in both HIV-infected and uninfected persons have appeared, including reduction in bone mineral density and mild decrease in creatinine clearance progressing to renal impairment in a small number of patients requiring drug cessation.[2] Since the introduction of highly active ART in the 1990s, an anchor drug (either a nonnucleoside reverse transcriptase inhibitor, a protease inhibitor, or an integrase inhibitor) in combination with 2 nucleoside reverse transcriptase inhibitors (tenofovir, emtricitabine/lamivudine as one of the preferred nucleoside combinations) have been recommended as effective ART and have stood the test of time for overall safety and efficacy. In fact, after weighing the available evidence, the 2013 World Health Organization consolidated guidelines recommended a once daily combination of tenofovir, emtricitabine/lamivudine, and efavirenz as the preferred regimen for initial therapy of HIV infection for all HIV-infected persons, including pregnant and breastfeeding women.[2]

Clinicians have choices in selecting ART treatment strategies for prevention in serodiscordant couples, between PrEP for the seronegative partner and ART for the seropositive partner, and in both cases with exposure to tenofovir with emtricitabine/lamivudine as the preferred nucleosides. How will the findings reported by Mugo et al[6] influence that choice? There is a clear difference in the concept of risk of adverse outcomes between exposures to these drugs in HIV-negative vs HIV-positive persons with many favoring the burden of more risk, albeit small to the HIV-infected person. Cross-study comparisons should be made cautiously; however, effective ART for HIV-infected persons has a 96% (95% CI, 77%-99%) reduction in transmission based on the HPTN 052 trial[8] and a 75% (95% CI, 55%-87%) reduction in transmission in the Partners PrEP study.[7] The conservative clinician's choice in this difficult decision of a possible harm signal for pregnancy outcomes will be to target ART to the HIV-infected partner, especially men in a heterosexual relationship, and to reserve PrEP for women who may have other unprotected exposures outside the primary relationship. These women should also be offered effective contraception. Clinicians should discuss the various risks and benefits of PrEP strategies to help patients make informed decisions.

The 2014 IAS-USA recommendations[1] highlight the importance of providing accurate information and counseling around prevention as an integral part of treatment provision, particularly in the context of providing PrEP and treatment as prevention. Fewer than half of the patients receiving ART in a US study[9] had received prevention counseling from their health care professionals in the previous 12 months. Clinicians have a responsibility to ensure patients are equipped to make informed decisions about how they manage risk, and to choose the combination of prevention methods that suit their individual circumstances, values, and preferences. Physicians and other health care professionals and workers responsible for providing this counseling and support should be adequately trained in the skills required to deliver this important aspect of care.

Implementation of biomedical interventions for prevention as part of a combined approach significantly strengthens the response to HIV. This expansion of prevention options must not be at the expense of deprioritizing behavioral or community-led prevention efforts. Instead both of these approaches should be recognized as being complementary and interdependent: behavioral approaches are required to support the effectiveness of ART, PrEP, and postexposure prophylaxis[10]; biomedical interventions contribute to prevention through mechanisms that behavioral interventions cannot. Established community-led approaches can support and be used in delivering biomedical interventions. Incorporating prevention within services that have historically focused on treatment may be challenging in some cases. The 2014 IAS-USA recommendations[1] reinforce the need for physicians, other clinicians, and health care workers to be supported so they can fulfil their responsibilities in effectively providing patients with behavioral and biomedical strategies for HIV prevention.

ARTICLE INFORMATION

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