Long-acting injections for HIV prevention among women in sub-Saharan Africa

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See Articles page 1779

Women in sub-Saharan Africa are one of the groups at highest risk of HIV in the world, encompassing 38% of new cases globally.[1] Multiple HIV prevention modalities have been developed and trialled in women in sub-Saharan Africa with limited success. Tenofovir vaginal gels showed initial promise with a 39% overall reduction in HIV infection,[2] but later trials showed no evidence of protection.[3] Two clinical trials of dapivirine vaginal rings showed an overall 27–31% risk reduction.[4,5] Daily oral pills containing tenofovir disoproxil fumarate are currently the standard for pre-exposure prophylaxis (PrEP).[6] Although oral PrEP is effective if taken regularly,[7] clinical trials in women in sub-Saharan Africa show variable protection ranging from 0% to 75%.[8,9] All of these studies highlight poor adherence as a primary driver of low protection, supported by clear adherence–efficacy associations.

Long-acting injections are a promising option to circumvent adherence challenges with PrEP. In *The Lancet*, Sinead Delany-Moretlwe and colleagues report findings from the HPTN 084 study,[10] a phase 3, randomised, controlled, superiority trial comparing intramuscular cabotegravir injections every 8 weeks with daily tenofovir disoproxil fumarate plus emtricitabine (TDF-FTC) pills. The study was conducted in seven countries in sub-Saharan Africa, in which 3224 women aged 18–45 years at risk of HIV were randomly assigned (1:1) to active cabotegravir injections plus placebo pills, or active TDF-FTC pills plus placebo injections, after an initial oral lead-in period to confirm cabotegravir tolerability. Delany-Moretlwe and colleagues observed 40 incident infections over 3898 person-years, with four in the cabotegravir group and 36 in the TDF-FTC group, which corresponds to an 88% lower risk of HIV infection for women in the cabotegravir group relative to the TDF-FTC group. This figure was revised to a 91% lower risk after a post-hoc analysis that excluded a baseline infection. Overall, the authors concluded that, although both cabotegravir injections and TDF-FTC pills were generally safe, well tolerated, and effective, cabotegravir was superior to TDF-FTC in preventing HIV infection in the study population.

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Delany-Moretlwe and colleagues did a detailed analysis of the four seroconversions for the cabotegravir group, which was particularly illuminating: two had not received any cabotegravir injections, one was retrospectively found to have been infected with HIV at baseline, and one occurred after a delayed injection visit. By comparison, all 36 infections in the TDF-FTC group were classified as incident infections. Underlying the high efficacy observed for cabotegravir, Delany-Moretlwe and colleagues report better adherence for the cabotegravir group than for the oral TDF-FTC group. 93% adherence was observed in those receiving injections, compared with only 18% for oral TDF-FTC (≥4 doses per week over the past month as measured by tenofovir-diphosphate (TFV-DP). Comparatively, HPTN 083, the sister clinical trial among men who have sex with men and transgender women in the USA, Latin America, Asia, and Africa reported a higher TDF-FTC adherence (72% as measured by TFV-DP) and a lower risk reduction (66%) for cabotegravir versus TDF-FTC than did the present study.[11] These differences highlight the potentially greater barriers that sub-Saharan African women face in taking pills, and suggest that, relative to daily oral PrEP, cabotegravir injections might have an even greater impact on reducing HIV in women in this context.

HPTN 084 was stopped early due to efficacy, with a median follow-up time of 1·24 years. Adverse events and discontinuation were relatively similar across both

TDF-FTC and cabotegravir groups. Effects of long-term use of cabotegravir will be important to assess, as this injectable form of PrEP could be used for several years. Specifically, in a population where the prevalence of cardiovascular disease is high, cabotegravir-associated weight gain should be monitored. In addition, although no integrase strand transfer inhibitor resistance mutations specific to the mechanism of action of cabotegravir were observed in this study, the risk of cabotegravir resistance will be important to ascertain in real-world settings with non-optimal adherence.

This well designed study shows tremendous potential for reducing HIV infections among women in sub-Saharan Africa and globally. Injections that last 2 or 3 months are among the most popular forms of contraception in sub-Saharan Africa, and women in HIV prevention trials have communicated a preference for similar long-acting HIV prevention options.[12] From a service delivery standpoint, once implementation strategies around the required oral lead-in period are optimised, cabotegravir injections could be easily administered alongside existing contraceptive injections. Although there is still space for innovation in both novel formulation and implementation of existing HIV prevention technologies, cabotegravir injections offer much promise over currently available options and should be prioritised for those at high risk of HIV infection.

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