Making waves: safety and efficacy of ART in women

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Information about the safety and efficacy of newer HIV treatment often lags behind for women, despite the fact that women now account for more than half of all HIV infections globally. Women are under-represented in clinical trials, comprising only 19% of participants in antiretroviral treatment (ART) studies despite efforts to correct this imbalance.[1] Women and men might differ with regard to drug pharmacokinetics,[2] toxic effects, comorbidities, and sociobehavioural factors related to ART (including adherence),[3] lending urgency to include both women and men in clinical HIV research.

The registrational clinical trials for the three most recently approved integrase strand transfer inhibitors, raltegravir, dolutegravir, and elvitegravir, were done in predominantly male populations, with enrolment of women rarely exceeding 25%.[4,5] When these drugs become more widely used globally they will be used in much higher proportions of women. In this issue of *The Lancet HIV*, Kathleen Squires and colleagues[6] report the results of a randomised clinical trial comparing tenofovir and emtricitabine combined with either elvitegravir with cobicistat or ritonavir-boosted atazanavir done in 575 antiretroviral treatment-naive women enrolled from sites in several countries. The findings from the trial are notable in that they explored both virological and other long-term outcomes.[7] The results of this study confirm the virological superiority of the integrase inhibitor inhibitor regimen, driven in part by tolerability advantages over the protease inhibitor regimen. These findings add further support to the US Department of Health and Human Services ART Guideline designation of the preferred status for elvitegravir plus cobicistat.

In addition, the study assessed changes in bone density and body fat, important issues for long-term health. Notably, trunk fat increases, as measured by dual energy x-ray absorptiometry, were greater in women randomised to the protease inhibitor based regimen compared with those receiving the integrase inhibitor regimen. This is by contrast with previous results in which raltegravir—another integrase inhibitor—was shown to have similar amounts of fat gain compared with atazanavir.[8] Whether the lower fat gain is a specific advantage of elvitegravir will require a direct comparison and it will be important that these comparisons are done among women as well as men.

The rate of pregnancy in female participants in recent HIV prevention or treatment trials ranges from 4–10 per 100 woman-years,[9] even though most trials exclude women who plan or wish to become pregnant during the study period, and many studies facilitate family planning. An important aspect of the study by Squires and colleagues[6] was the fact that women who became pregnant were allowed to continue in the study on randomised treatment. Although not all women who became pregnant were followed up, it was notable to see that 25% experienced early pregnancy loss. Although this spontaneous abortion rate in a very small sample might not exceed the background rate in non-HIV-infected women[10] (nor in HIV-infected women not taking ART[11]), it provides a reminder of the dearth of information about the safety of newer antiretroviral agents during pregnancy. More than 1·5 million HIV-infected women deliver annually, and most of these women now receive ART antepartum.[12] As the roll out of ART for life expands globally and more women conceive on ART, it is imperative that we collect adequate safety and efficacy data for women throughout the life span. Several studies have shown increased rates of adverse pregnancy outcomes (preterm birth, stillbirth, small for gestational age, and in some instances spontaneous abortion) associated with HIV infection or with ART, or both, in pregnancy,[13] and some regimens might be safer than others with regard to adverse pregnancy outcomes.[14,15] Only through the conduct of comparative clinical trials and high-quality observational studies will we learn whether there are differences due to specific antiretroviral drugs, or to the timing of ART initiation in pregnancy.

Women-specific ART trials add important data to the safety profile for new antiretroviral drugs as well as confirming data for efficacy. These studies should allow women of all ages to enrol and those who become pregnant should be allowed remain on treatment and in follow-up extended through delivery. The lag-time in obtaining this information needs to shorten.

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