Title

Long-term use of ART in African women of reproductive age

Journal

The Lancet HIV, 9(6)

ISSN

2352-3018

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Publication Date

2022-06-01

DOI

10.1016/s2352-3018(22)00061-3

the ODDYSEY[8] studies, which were done in the same scenario. An elegant virological analysis in DAWNING characterised in vitro dolutegravir resistance as a change of more than ten-fold with reduced replication capacity.[7] Therefore, the barrier against resistance to dolutegravir when administered with two mostly inactive NRTIs is not optimal. A more detailed analysis of dolutegravir resistance in NADIA is eagerly awaited.

Emergence of dolutegravir resistance in integrase-naive patients on second-line ART in Africa is of concern and needs urgent attention, especially when considering the fact that no participants developed treatment resistance in the ritonavir-boosted darunavir group. Transitioning to dolutegravir in both first-line and second-line ART is a WHO priority and will save many lives, and preserving activity of the drug by preventing the spread of integrase resistance is of paramount importance.[9] Growing resistance to HIV drugs in Africa is threatening progress made in the global fight against the virus, and integrase resistance in particular must be tackled. Therefore, further studies are needed to fine-tune the activity of second-line regimens and mitigate integrase resistance selection in low-income countries. Meanwhile, ritonavir-boosted darunavir merits consideration for an expanded role in second-line ART in the public health approach in Africa.

JML has received payments or honoraria for lectures, presentations, or speaker's bureaus from Janssen-Cilag, Gilead Sciences, and ViiV Healthcare, outside of this linked Comment.

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Published **Online**
April 27, 2022
https://doi.org/10.1016/S2352-3018(22)00061-3

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There is strong evidence that antiretroviral therapy (ART) for cisgender women of reproductive age living with HIV reduces vertical HIV transmission[1] and improves women's health and survival.[2] However, there is a dearth of research on the long-term (≥5 years) effects of ART in reproductive-age women who started ART during pregnancy.

From 2011 to 2016, PROMISE, a multi-country randomised clinical trial from 13 African sites and one non-African site, showed low rates of vertical HIV transmission when pregnant women living with HIV received combination ART.[3,4] In *The Lancet HIV*, the follow-on PROMOTE study by Taha E Taha and colleagues[5] started in 2016 when the PROMISE follow-up ended. Investigators followed up on women and their children in eight African sites from four countries, including Uganda, Malawi, Zimbabwe, and South Africa. The study enrolled 1987 mothers and 2522 children. The median follow-up time was 42 months in mothers and 36 months in children. Retention rates were very high in the study (85% at 42 months for children).[6] Two notable strengths of this study were the long follow-up period (using standard of care clinical follow-up time of visits every 6 months) and the inclusion of women from multiple, diverse settings, and countries across the region.

Taha and colleagues'[5] results are encouraging in that they show that African cisgender women are willing to be a part of a long follow-up period from 2010–11 (when they originally enrolled in PROMISE) to 2021.

Additionally, the investigators show that these African women living with HIV continued using ART for years after pregnancy while maintaining high adherence and achieving high levels (>90%) of viral suppression at the 42 months follow-up in most study sites, except for sites in Malawi, Harare (Zimbabwe), and Durban (South Africa). The PROMOTE study showed that losses to follow-up were minimal, adherence to ART was high, and there was evidence that these women benefited from ART use—reflected in the improvement of health indicators over time, including high levels of fertility and self-reported health. Furthermore, perinatal transmission of HIV among women who had subsequent pregnancies is incredibly low (three new HIV perinatal infections were reported, mostly due to inadequate ART adherence).

Importantly, investigators followed up on the cohort of women on ART for 3–4 years and they did not identify any major safety concerns. Life-threatening events related to ART use were rare; however, four of the maternal deaths might have been associated with efavirenz-induced liver toxicity. In children (median follow-up of 3 years), life-threatening events were also rare. Mortality rates for both mothers and children were low compared with background rates in most of these settings in populations with HIV and the general population.

However, this study highlights two primary areas of concern. First, approximately 11% of women had detectable viral load at their last visit, and over 200 women and 300 infants were not retained and might have been lost to follow-up. The potential consequences of suboptimal adherence (eg, vertical HIV transmission, inflammation, and related non-communicable disease) are reasons for concern. The authors expect adherence to improve as women switch to better regimens, such as dolutegravir, which is being rolled out to pregnant women in the region.[7] Second, the study found a relatively high frequency of abortions or miscarriages in some sites (eg, in Soweto and Uganda). In addition, fertility intentions (defined as wanting more children) were low across all sites, except for Kampala (Uganda), highlighting the urgent need for ongoing contraception services and integrated, strengthened sexual and reproductive health services in post-partum care for women living with HIV.

The PROMISE and PROMOTE studies showed that longitudinal, multicountry studies of mothers and their infants are feasible in sub-Saharan Africa. First, this study is crucial to provide evidence to policy makers about the importance of interventions to improve ART continuation and adherence among women of reproductive age living with HIV. Second, this study serves as a model for funders and researchers seeking to evaluate the longitudinal impact of new ART regimens (eg, long-acting ART),[8] new prevention technologies (eg, long-acting pre-exposure prophylaxis[9]), and multiple prevention technologies (products capable of addressing multiple sexual and reproductive health needs) for and with women who are pregnant or in the post-partum period.[10]

I declare grants and non-financial support from Gilead and personal fees from ViiV.

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