HIV, ART and fertility in sub-Saharan Africa: pieces still missing in the jigsaw puzzle

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Quantifying and understanding the effects of HIV infection and antiretroviral treatment (ART) on fertility is essential for accurate global and national HIV estimates – and especially for estimates of key indicators of the HIV epidemic in children including coverage of prevention of mother-to-child transmission (PMTCT) and paediatric treatment programmes, the contribution of long-term survival from mother-to-child transmission to HIV prevalence at adolescent and young adult ages, and the growing numbers of HIV-exposed uninfected children, for whom, exposure to certain ART drugs at conception may increase the risk of neural tube defects[1]. Equally – if not more – important, this information is needed to ensure that women on ART get appropriate counselling and access to family planning and sexual health services.

Prior to ART, lower fertility in HIV-positive women in sub-Saharan Africa was well-documented[2-5]. The relationship between HIV and fertility varied with age – in the youngest age-group (15-19 years), fertility was higher among HIV-positive women, due to selection of sexually-active women, while, at older ages (25 years and above), the fertility of HIV-positive women became progressively lower than that of their uninfected counterparts. Biological and socio-behavioural mechanisms were hypothesised to explain HIV subfertility. Biological factors included the physiological and immunological effects of HIV infection, coinfections with other STIs, and lower semen quality in male HIV-infected partners[6-8]. Socio-behavioural factors included reduced sexual activity in HIV-positive women compared to HIV-negative women due to poor health, greater widowhood and marital dissolution, and low rates of remarriage[9-11].

It had been widely anticipated that ART scale-up would attenuate many of these mechanisms; thereby lessening subfertility in HIV-positive women[12]. For example, the physiological and immunological effects of HIV in lowering fertility could be reduced if ART lessens the progression and severity of women's HIV disease. Reduced widowhood and divorce, together with increased sexual activity due to improved health, could increase exposure to pregnancy for HIV-positive women compared to the pre-ART era. Fertility desires might also change. However, a systematic review by Yeatman and colleagues[13], which examined data collected largely during periods of ART scale-up, found a mixed picture and concluded that fertility in HIV-positive women may increase after the first year on ART but remains lower than in HIV-negative women of the same age.

In this issue of the *Journal of Infectious Diseases*, Johnson and colleagues[14] employ novel methods to compile and analyse a large dataset drawn from routine programme records in the Western Cape in South Africa to provide further insight into the impact of ART on fertility. Using South Africa's unique patient identifier, they linked data from women's antenatal care visits with data on HIV status and ART. For women with evidence of at least one pregnancy, they used time from date of first pregnancy outcome to date of second pregnancy conception to compare pregnancy rates by HIV infection and ART status. Consistent with the studies conducted in the pre-ART period, the authors found that

pregnancy rates in HIV-positive women not on ART were lower than in HIV-negative women. However, they also found that pregnancy rates in HIV-positive women on ART were higher than those in HIV-negative women.

The new study is important in that it strengthens the evidence that, among women with a recent pregnancy, the subsequent pregnancy rate in women on ART is higher than the rate for infected but ART naïve women; and adds to the literature a finding that, in this population, their pregnancy rate also exceeds that in uninfected women. Unfortunately, however, key questions remain regarding fertility differentials in women who do not have a recent history of pregnancy and, therefore, about the generalisability of the study findings to women as a whole in the population. Included in the Yeatman review, the only clinic-based studies which yielded a similar finding that, among HIV-positive women, women on ART had higher pregnancy rates than those who were ART-naïve, were also from populations of women who were recently pregnant[15] or pregnant at enrolment[16]. The second of these studies found no such difference in pregnancy rates for HIV-positive women who were not pregnant at enrolment[16]. In one of two population-based studies[17], a higher incidence of pregnancies was found in HIV-positive women on ART compared to those who were ART-naïve; but, women not at risk of pregnancy, including those using hormonal contraceptives were excluded from the analysis which may have resulted in selection bias. In the second population-based study, no difference was found between HIV-positive women on ART compared to those who were ART-naïve[18]. These studies, therefore, taken together with the new study in South Africa, appear to show that ART raises fertility in HIV-positive women who have recently been pregnant – and thereby have demonstrated that they are already fecund despite being infected – but that ART has little or no impact on fertility for those who have not been pregnant recently.

For HIV-positive women who have had a recent pregnancy, as in other studies[15, 16], Johnson and colleagues found that pregnancy incidence rates were higher in women on ART than in ART naïve women even after controlling for CD4 count. This suggests that there are mechanisms independent of physiological improvements in health that contribute to increased pregnancy incidence. The authors point to reasons such as increased fertility desires or increased motivation to start ART in women who want further children. Another possibility is that ART may lower the efficacy of some hormonal contraceptives[19] which are used by 31% of women in the Western Cape[20]. Currently, it is unknown whether the high pregnancy rate in HIV-positive women on ART compared to uninfected women will continue or whether this is a tempo effect such that completed family size will eventually be the same in the two groups.

For HIV-positive women who have not had a recent pregnancy, there are a number of mechanisms that could limit the effect of ART in reversing HIV-associated subfertility. These include that these women may have no sexual partner, may be using condoms or other effective forms of contraception, or may be infertile – perhaps due to a history of other STIs such as Gonorrhoea or Chlamydia[21].

The impact of ART on fertility at the population level will be a combination of its impact on the fertility of HIV-positive women who have and have not had recent pregnancies. Whilst Johnson and colleagues provide evidence that ART increases fertility in women who have recently been pregnant, once women who have not recently had a child or who have never been pregnant are included, the difference in fertility between women on ART and HIV-negative women may disappear or be reversed. The end result may also depend on the composition of the population on ART in terms of how they enrol into care (via antenatal or counselling and testing services) and overall ART coverage.

A number of vital pieces of the jigsaw therefore remain missing for modelling the population-level effects of ART on fertility and providing reliable estimates of the impact of HIV, PMTCT and ART on children. In addition to the above, further pieces that remain poorly understood include the possibilities that: 1) initially ART scale-up may increase the fertility of women who are not yet on

treatment – in absolute terms and relative to that of HIV-negative women – due to selective initiation on ART of women at more advanced stages of infection; 2) changes in policy over time can change the population on ART; for example, the change in WHO guidelines to option B+, where women are immediately offered treatment for life regardless of their CD4 count, may have increased the proportion of healthier, recently-pregnant women on ART; 3) the impact of ART may vary by region due to differences in the underlying reasons for HIV subfertility; and 4) ART scale-up may have indirect effects on the fertility of HIV-negative women – for example, through its effects in reducing HIV transmission and in increasing risk compensation and unprotected sex.

The most effective way to fill in these missing pieces of the puzzle and build on the study by Johnson and colleagues could be to collect and analyse more data in prospective general population HIV sero-surveys, as has been done in Zimbabwe and Malawi[18, 22] and may be possible in other studies in the ALPHA network[23] particularly those with links to routine data from local CTC clinics. This would allow further comparisons of fertility rates between HIV-positive women – by HIV diagnosis and ART status – and uninfected women, investigation of potential mechanisms of ART impact in these groups, and evaluation of the biases inherent in analyses of clinic-based data. Data from CTC clinics could provide reliable information on patterns and trends in the composition of women on ART (by age, CD4 count, pregnancy status at initiation) and on how these women were referred for initiation. This could also help us to understand the reasons for observed fertility differences (or lack of differences) between women on and off ART, and to infer how the population not seen at CTC clinics might be changing. Networks such as the International Epidemiology Databases to Evaluate AIDS (IeDEA) Network[24], an international collaboration between CTC clinics including clinics in sub-Saharan Africa, are ideally placed to look at such data.

Potential conflicts of interest.

Milly Marston: No reported conflicts.

Simon Gregson: Reports shares in GlaxoSmithKline and Astra Zeneca.

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