The Potential Impact of Antiretroviral Therapy on Fertility in sub-Saharan Africa

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In SSA, HIV is predominantly transmitted through heterosexual intercourse [1], which further entangles the impact of the HIV epidemic on fertility. The common pathway suggests that both the risk of HIV infection and pregnancy may share similar risk factors and distribution in the population. Yet, substantial evidence indicates that HIV-infected women in SSA have between 25% and 40% lower fertility than noninfected women [3,4•].

This evidence for reduced fertility arises from settings with limited (or no) access to HIV/AIDS treatment. Recently, however, access to antiretroviral (ARV) treatment in SSA is improving considerably [5,6]. The potential impact of ARV therapy on the survival and quality of life of individuals with HIV infection has been demonstrated in numerous studies from developed and developing countries [7–10]. As ARV therapy becomes increasingly accessible in SSA, it is important to understand whether and how the associated clinical improvements correspond with changes in the incidence of pregnancy and fertility among women with HIV infection.

Thus, the purpose of this article is to review the literature regarding the potential impact of ARV therapy on fertility in SSA. We begin by briefly reviewing the evidence for lower fertility among women with HIV infection (not on therapy) compared with uninfected women. Then, we examine the literature on ARV therapy and fertility in SSA. Owing to limited empirical evidence from this setting, we review the evidence from developed countries and discuss implications for developing regions. Next, we use Bongaart’s proximate determinants of fertility framework (adapted for conditions of a generalized HIV epidemic) [11,12] to examine the underlying mechanisms through which use of ARV therapy may impact the fertility of women with HIV infection. A conceptual framework is proposed to guide future research aimed at understanding how widespread use of ARV therapy may impact fertility in SSA.

Introduction
Women of reproductive age comprise 46% of the world’s HIV-infected adult population. The majority live in sub-Saharan Africa (SSA), where approximately 14 million women of child-bearing age are currently living with HIV/AIDS [1]. HIV infection in these women raises important public health concerns about the incidence of pregnancy. Such concerns relate to the survival and health of the mother and the health of her baby, including risk of vertical disease transmission, orphanhood, and other adverse pregnancy outcomes [2].

HIV and Fertility in SSA
In societies with low contraceptive use, women with HIV infection have lower fertility than noninfected women.
This finding is explained by both the direct biological effects of HIV on the fecundity of infected women and the indirect impact of the virus on the behavioral determinants of fertility [3,4•].

Two review articles have examined the relationship between HIV and fertility in SSA [3,4•]. In 1998, Zaba and Gregson [3] reviewed six studies in SSA to conclude that women with HIV infection have between 25% and 40% lower fertility than noninfected women for most age groups. Only in the youngest age group (15–19 years) is HIV-infection associated with higher fertility, presumably due to selection for early sexual activity. A more recent review of an additional 13 studies similarly concluded that HIV-infected women in SSA experienced lower fertility than their noninfected counterparts [4•]. The authors estimated that each 1% increase in population prevalence of HIV in SSA countries results in a population-attributable decline in fertility of 0.37% (95% CI, 0.30%–0.44%) [4•]. The investigators used mathematical modeling to demonstrate the substantial impact of such a reduction in fertility. They estimated that the combined effect of increased mortality among women with HIV infection, and an assumed 20% reduction in fertility resulted in 700,000 fewer births in Uganda between 1980 and 2000.

These findings have been further substantiated by recent studies from SSA that report similar decreases in fertility among women with HIV infection compared with uninfected women [13,14]. Recent studies have also shown that fertility decreases dramatically by disease progression [14,15] and decreasing CD4+ cell counts [14–16].

ARV Therapy and Fertility in SSA
Between June and December 2004, the number of people on ARV therapy in SSA doubled from 150,000 to 310,000 [6]. Although coverage varies dramatically by country, in Botswana, Namibia, and Uganda greater than 25% of those who need treatment are receiving it; 13 other countries in the region have greater than 10% coverage [6].

ARV therapy becomes increasingly accessible in SSA, the associated improvements in health, quality of life, and survival are anticipated to influence both the biological and behavioral fertility determinants of infected women. There remains, however, little empirical evidence to support this claim due, in part, to the recency of ARV treatment programs in the region.

ARV Therapy and Fertility in Developed Countries
Research in developed countries suggests that HIV is associated with a decline in fertility and that ARV therapy reverses this decline. Studies conducted before the widespread availability of ARV therapy have shown that HIV-infected women in developed countries are less likely to become pregnant [17–21] and give birth [21,22] compared with uninfected women. Studies also report that the incidence of pregnancy and livebirth declines as AIDS develops [23] and that women with HIV infection suffer higher rates of adverse outcomes (including induced and spontaneous abortions) than uninfected women [19–21].

Current hypotheses suggest that the observed decline in fertility will be largely reversed with the introduction of highly active antiretroviral therapy (HAART); however, available studies have yielded somewhat differing results.

Blair et al. [24•] found that HIV-infected women in the United States were 20% more likely to become pregnant in the “HAART era” (1997–2001) than in previous years (1992–1996) (adjusted relative risk 1.2; 95% CI, 1.1–1.4). The higher pregnancy rate during the HAART era was thought to be due to both increased survival times and delayed progression to AIDS, which resulted in more opportunities to become pregnant.

Another American cohort study of women with HIV infection followed between 1994 and 2002 revealed somewhat different results. Massad et al. [25] reported that use of ARVs at baseline was associated with a decreased incidence of pregnancy compared with HIV-infected women not on therapy (odds ratio [OR] = 0.34; 95% CI, 0.49–0.98 for mono- or combination therapy; OR = 0.34; 95% CI, 0.03–4.28 for HAART). The study also reported that induced abortion became less common in the later HAART era (1999–2002) compared with earlier periods. The net impact of these findings (ie, decreased incidence of pregnancy and increased incidence of livebirth) on fertility in the HAART era remains uncertain.

Finally, a European prospective cohort study of women with HIV infection followed between 1985 and 1998 found no statistically significant increased trend in the age-adjusted incidence of pregnancy after HIV diagnosis over time [17]. In particular, the rate of pregnancy did not change in the HAART era (1997–1998) compared with earlier periods. However, because the study included only the first 2 years of widespread HAART use, it may be too early to conclude that HAART did not influence reproductive decision-making.

Delineating the impact of HAART on fertility is complicated by the lack of information about changes in other determinants of fertility over the follow-up period of these studies. It is unclear, for example, whether the women altered contraceptive or sexual practices or experienced changes in other variables important to understanding fertility differentials. Indeed, an observed increase in fertility may be a reaction to the availability of treatment to prevent mother-to-child-transmission (MTCT), rather than to the impact of HAART. Furthermore, the overall low fertility rate and HIV prevalence in these settings, compared with rates in SSA, may minimize the observed differential impact of ARVs on fertility. There may also be important cultural differences that influence fertility decisions in various contexts, which include societal expectations to bear children [26]. Thus, although infor-