Impact of ART on the Fertility of HIV-Positive Women in Sub-Saharan Africa

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Abstract

Objective: Understanding the fertility of HIV-positive women is critical to estimating HIV epidemic trends from surveillance data and planning resource needs and coverage of prevention-of-mother-to-child transmission services in sub-Saharan Africa. In light of the considerable scale-up in antiretroviral therapy (ART) coverage over the last decade, we conducted a systematic review of the impact of ART on the fertility outcomes of HIV-positive women.

Methods: We searched Medline, Embase, Popline, PubMed and African Index Medicus. Studies were included if they were conducted in sub-Saharan Africa and provided estimates of fertility outcomes (live births or pregnancies) among women on ART relative to a comparison group.

Results: Of 2070 unique references, 18 published papers met all eligibility criteria. Comparisons fell into four categories: fertility of HIV-positive women relative to HIV-negative women; fertility of HIV-positive women on ART compared to those not yet on ART; fertility differences by duration on ART;

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and temporal trends in fertility among HIV-positive women. Evidence indicates that fertility increases after approximately the first year on ART, and that while the fertility deficit of HIV-positive women is shrinking, their fertility remains below that of HIV-negative women. These findings, however, were based on limited data mostly during the period 2005-2010 when ART scaled up.

Conclusions: Existing data are insufficient to characterize how ART has affected the fertility of HIV-positive women in sub-Saharan Africa. Improving evidence about fertility among women on ART is an urgent priority for planning HIV resource needs and understanding HIV epidemic trends. Alternative data sources such as antenatal clinic data, general population cohorts and population-based surveys can be harnessed to understand the issue.

Keywords HIV, sub-Saharan Africa, antiretroviral therapy, fertility, pregnancy, births, systematic review

Introduction

The fertility of HIV-positive women is a principal determinant of the need for prevention of mother-to-child transmission (PMTCT) and paediatric HIV services. Understanding the relationship between HIV and fertility, and variation in this relationship by age, is essential for using HIV prevalence among pregnant women to estimate and track trends in the HIV prevalence of the general population over time (1-3). Although much is known about the relationship between HIV and fertility in sub-Saharan Africa in the absence of anti-retroviral therapy (ART) (3-5), it remains unclear just how the spread of treatment throughout the region has affected this important relationship.

Researchers have long recognized the fertility-suppressing effect of HIV on fecundity, the physiologic ability to have children (3, 6, 7). Because the biological effects of HIV on fecundity increase with advancing infection (8), they are most pronounced in older HIV-positive women who are likely to have been infected years earlier. There are also behavioural effects of HIV on fertility that can be either volitional (i.e., done with an explicit fertility motivation) or non-volitional. The former include changes in contraceptive use intended to prevent or encourage a pregnancy while the latter include changes in divorce, widowhood and remarriage patterns due to HIV that indirectly affect fertility.

Before the widespread availability of ART, the fertility of HIV-positive women throughout sub-Saharan Africa was lower than that of similar HIV-negative women due to a combination of biological and behavioural mechanisms. Population-based HIV surveillance studies revealed variation in the

so-called 'fertility discount' by age, however. At younger ages (<20), fertility was higher in HIV-positive women due to selection effects (i.e., selection into sexual activity among HIV-positive women). Above age 20, fertility among HIV-positive women was 25-40% lower than among HIV-negative women (3, 5). More recently, using Demographic and Health Survey (DHS) data from before the widespread availability of ART (2003-2006), Chen and Walker (4) showed that the age-specific fertility ratio decreased with age until the fertility of HIV-positive women was approximately half that of HIV-negative women in the 40-44 age group.

With the growing availability of ART throughout much of sub-Saharan Africa, the relationship between HIV and fertility will change (9). Precisely how quickly and to what extent change will occur remains unclear because of the recent nature of expanded ART coverage. Given high levels of underlying fertility in much of the region, small changes in any factor can carry large implications for estimates of PMTCT need and service coverage. Since estimates of paediatric HIV infections are derived using models based on the number of HIV-positive pregnant women and coverage of PMTCT, this can dramatically affect estimates of children living with HIV. Changes in the fertility discount by age could affect interpretations of prevalence trends in antenatal care (ANC) and PMTCT clinic surveillance.

To better understand the effect of ART on the fertility of HIV-positive women in sub-Saharan Africa, we conducted a systematic review of the current literature, using the term "fertility" in its demographic sense to refer to fertility outcomes: live births and pregnancies.

Methods

Search strategy

This systematic review conforms to the PRISMA guidelines (Supplementary Appendix 1) (10). On 14 October 2015, Medline, Embase, Popline, and African Index Medicus were searched using combinations of search terms without language or date restrictions. A top-up search for non-Medline records was additionally run in PubMed. The review was updated on 26 May 2016. The following concepts were included in the search: antiretroviral therapy (including ART, HAART, cART) AND fertility outcomes (including pregnancy, birth, reproductive health or fertility). Searching for all concepts in subject headings, title and abstract simultaneously proved to have very poor specificity. A faceted approach was therefore used, in which the return of each concept in free-text and subject headings was tested iteratively and the most precise combinations selected for inclusion in the final search. In the final search, concepts were combined as follows:

- Antiretroviral therapy [subject headings and free-text in title and abstract]
- Fertility outcomes [subject headings only]
- 1 AND 2
- Antiretroviral therapy [subject headings and free-text in title only]
- Fertility outcomes [title and abstract free-text]
- 4 AND 5
- 3 OR 6

The combination of fertility terms appearing anywhere and ART terms appearing in the abstract only was found to have very poor specificity and was therefore removed from the final strategy. As the review focus was antiretroviral therapy, terms for HIV infection or seropositivity were not included independently. Where possible, animal studies and studies on assisted reproductive techniques were excluded. The full search strategy is shown in Supplementary Appendix 2; there is no formal review protocol. Faceted searching was not possible in Popline and African Index Medicus, so a simplified version of the strategy was used. The bibliographies of all retained studies were also searched by hand.

Eligibility criteria

Studies were eligible for inclusion if they were conducted in sub-Saharan Africa, contained estimates of fertility outcomes (i.e., birth or pregnancy) for HIV-positive women on ART (or during a post-ART time period) over a defined period of time, and permitted a comparison of the fertility of HIV-positive women to another population.

Study selection

Titles and abstracts were screened by one author and full texts were sought for potentially relevant publications. In total, 2677 initial references were screened for eligibility and excluded for being duplicates (n=607) or through title (n=1647), abstract (n=375) or full-text review (n=31). An additional study that met criteria for inclusion was identified by checking the references of other reviewed studies (see Fig. 1).

Data extraction and analysis

Data were extracted on: study setting; time period covered; sample description; design; comparisons made; outcome; and key findings. Because fertility is shaped not only by biology, but also by behavior and the social and cultural norms of a specific context, the review focused on the *relative* differences in fertility adjusted for age rather than on absolute levels of pregnancy rates that may not be generalizable beyond a particular study setting. Substantial heterogeneity in comparators, sample inclusion criteria, and control variables prevented the meaningful pooling of statistics.

Quality assessment

In line with the PRISMA guidelines, the risk of bias was assessed, focusing on the comparability of comparison populations, selectivity and size of sample, method of measuring pregnancy or birth, and appropriate handling of age. Given the strong and non-linear relationship between age and fertility, and that women on ART are older on average, it is essential to stratify or use age-standardized comparison populations to reduce biases introduced by differences in age composition.

Results

After exclusions, the literature search identified 18 articles that met all study criteria (Table 1). Included articles offered at least one of four comparisons:

- (1) fertility of HIV-positive women on ART vs. fertility of HIV-negative women;
- (2) fertility of HIV-positive women on ART vs. HIV-positive women not yet on ART;
- (3) fertility of HIV-positive women by time on ART or time-varying CD4 count after initiation; or
- (4) fertility of HIV-positive women before and after ART was widely available.

Most studies were from a single setting, although five used data from multiple countries in the region (11-15). Data came from Uganda (9 studies), South Africa (4), Kenya (4), Malawi (2), Rwanda (2), Cote d'Ivoire (2), Zimbabwe (2), Zambia (1), Tanzania (1), Gambia (1), Mali (1), Guinea-Bissau (1), Nigeria (1), Burkina Faso (1), Benin (1) and Senegal (1). The included countries range widely in HIV prevalence (from 0.5% in Senegal to 18.9% in South Africa) (16) and total fertility rate (from 2.4 in South Africa to 6.4 in Mali) (17).

The majority of studies were conducted in HIV clinics (n=12) or as part of HIV outreach programs or studies (n=3). Only three studies used population-based samples: a study that was conducted among 12 communities in eastern Zimbabwe (1); one that drew from demographic and HIV surveillance sites in Uganda, Tanzania and South Africa (13); and another that used two rounds of the nationally-representative Malawi Demographic and Health Survey (DHS) (18). These studies were the only ones to contain data from a more representative sample of HIV-positive women, some of whom may not be enrolled in clinical care nor necessarily aware of their HIV positive status. Clinic-based studies, however, were better able to accurately assess ART status at the time of conception.

Fifteen studies used pregnancy incidence or prevalence as the main outcome. The three exceptions were a cross-sectional study from semi-urban Uganda that examined the likelihood of live birth and of pregnancy over the previous three years (19), and two of the population-based studies that used age-specific fertility rates and thus focused on live births rather than pregnancies (13, 18). Eight of the 16 studies measuring pregnancy used testing or clinical examination to determine pregnancy while the others relied on self-reported pregnancy, which will be biased toward established pregnancies and pregnancies that end in live birth. On the other hand, for estimates of the need for PMTCT and paediatric HIV, live births and more advanced pregnancies are the most relevant outcomes.

Studies covered a range of years from 1998-2013 with most person-years of data concentrated in the 2005-2010 period, a time in which ART access expanded rapidly in most settings. All studies included women from across the reproductive ages, although some (1, 11, 13, 18, 20, 21) handled age more thoroughly in analyses than others (see Table 1).

Fertility in HIV-positive vs. HIV-negative women

Only three studies (1, 13, 18) had a purposefully-selected HIV-negative comparison group, although two more made indirect comparisons to national level data (21, 22). Gregson and colleagues (1) found that in a period of increasingly good access to ART in Zimbabwe (2009-2011), the age-adjusted prevalence of pregnancy among HIV-positive women (not all of whom were aware of their status) was 75% that of HIV-negative women. With the exception of the youngest age group (15-24) in which fertility did not differ by HIV status, HIV-positive women had substantially lower pregnancy prevalence regardless of ART use.

Recently, Marston et al. (13) analysed data from four demographic and HIV surveillance sites in Uganda, Tanzania and South Africa. Using data from 59,440 women, the researchers found that the gap between the age-specific fertility rates of HIV-positive and HIV-negative women narrowed in the post-ART period. The narrowing was principally due to reductions in the fertility of HIV-negative women rather than to increases among HIV-positive women, whose fertility stayed steady or increased only slightly over the study period (depending on study site). Despite this narrowing, the age-adjusted fertility rate ratio of HIV-positive to HIV-negative women ranged between 0.57 (95% CI 0.64-0.83) and 0.83 (95% CI 0.78-0.87) across sites and followed the same age pattern as in the pre-ART period.

The findings from nationally representative cross-sectional data from Malawi support the aforementioned studies (18). Despite a relative increase in the fertility of HIV-positive women compared to HIV-negative women between 2004 and 2010, the fertility of HIV-positive women remained at least 25% lower in the latter time period (18). Two of these population-based studies (13, 18) lack data on individual ART use, and therefore cannot speak to the relative fertility contribution of women on ART and not on ART, which is important for estimating the need for PMTCT and paediatric HIV services.

Fertility women on ART and women not yet on ART

There was disagreement among studies on the pregnancy incidence of women on ART vs. HIV-positive women engaged in care but not yet on ART. Using data from a postpartum sample of women attending 11 urban HIV clinics in six sub-Saharan Africa countries, Myer et al. (11) compared the pregnancy incidence of women on ART to women in pre-ART care after adjusting for a number of variables including age and CD4 count at enrollment. Pregnancy incidence was 1.74 (95% CI 1.19–2.54) times greater among HIV-positive women who recently started ART than among women who had not yet done so. The same trend was noted across study countries although it was stronger in some than in others. Similarly, a community-based HIV care program in rural Uganda found that pregnancy incidence was twice as high among HIV-positive women on ART (23).

In contrast, a recent study from 26 HIV clinics in Uganda and Kenya found no difference in pregnancy incidence between women on ART and those not yet on ART. Importantly, these researchers adjusted for time-varying clinical stage and CD4 count and robustly accounted for loss to follow-up and death (14). Another study (24) similarly found no difference in the pregnancy incidence of women in an HIV-clinic in Kenya on a nevirapine-based ART regimen compared to women not yet on ART,

after adjusting for sociodemographic characteristics and time-varying CD4 count. This was similar to the findings of a Kenyan study of HIV-positive women in sero-discordant relationships (25).

Two studies found no difference in pregnancy incidence by ART (26, 27) and one found higher pregnancy incidence among women not yet on ART than among those on ART (15), but these studies did not adjust for sociodemographic or health differences between the groups.

Fertility differences by duration on ART

A common approach taken by clinic-based studies was to examine changes in pregnancy incidence by time on ART. Some studies prospectively examined women from their initiation on ART, while others included women who may have started ART before study enrollment but whose time of ART initiation was known. Most studies found significant variation in pregnancy incidence by ART duration. Tweya and colleagues (21), for example, found that pregnancy incidence was particularly low among women in an urban Malawian ART clinic during their first six months on ART. After those six months, fertility substantially increased among all age groups. One study from rural Uganda found that pregnancy incidence peaked 12 to 18 months after initiation (22), while another study from rural Uganda found peaks at 6 to 12 months and then again at 4 years, presumably due to a birth interval effect (28). In West Africa, data from ART clinics in six countries showed the highest pregnancy incidence in year four (12). In contrast, a study from Johannesburg, South Africa found no difference in pregnancy incidence by time on ART (29).

One study used time-varying CD4 count and adherence as a proxy for quality of ART use (20). This study from Johannesburg, South Africa found that pregnancy incidence increased among women on ART when their CD4 count was >100 cells/mm³ and with better adherence (20). The finding of this study is consistent with two others that found pregnancy incidence to be significantly higher among women who started ART at WHO Stage 1/2 rather than WHO Stage 3/4 (12, 21).

Temporal trends in fertility among HIV-positive women

Another approach examined trends in the fertility of HIV-positive women over time. The clinical cohort study from Kenya and Uganda found that pregnancy incidence was higher among HIV-positive women enrolled in clinical care in 2005-2006 than among women enrolled in 2001-2004 (Elul et al

2016). For women enrolled in 2007-2009, however, pregnancy incidence was no longer different from the earliest years after adjusting for compositional changes including ART use, CD4 count and age (as a linear variable).

The study using clinical cohort data from six West African countries (12) found that overall pregnancy incidence of women on ART increased over the time period (1998-2011). After adjusting for age, CD4 count, WHO clinical stage and hemoglobin at initiation, women who began ART between 2009-2011 had a 58% (95% CI 35-86) higher pregnancy incidence than women who began ART before 2005.

Finally, the population-based study from four demographic and health surveillance sites (13) found that the fertility of HIV-positive women, including those not engaged in care, stayed the same at two of the study sites and modestly increased at two other two sites over the pre-ART to post-ART periods. When interpreted against a background of secular declines in fertility, however, this stability represents increases in the fertility of HIV-positive vs. HIV-negative women (13).

Discussion

This systematic review examined the evidence for how the provision of ART has affected the fertility patterns of HIV-positive women and the broader relationship between HIV and fertility in sub-Saharan Africa. Current evidence suggests that: (1) fertility increases among women after they have been on ART for approximately one year; (2) fertility of women on ART is similar to comparable clinic populations of women not yet on ART when adjusted for health (e.g. CD4 count); but (3) remains somewhat lower than that of HIV-negative women.

However, the current evidence is insufficient to be confident in these conclusions. Fertility of HIV-positive women vs. HIV-negative women, appropriately accounting for age and ART use, is the gold standard comparison and what is required for robust answers to these questions. Unfortunately, only one study identified in the review included a purposely selected HIV-negative comparison population and data on ART use, and in this study ART use was self-reported and information about timing of ART initiation was not available (1).

Nonetheless, we can make general observations about the effects of ART on the fertility of HIV-positive women based on existing evidence. This suggests that women who access ART in the advanced stages of disease increase their fertility after a period of time, likely due to improvements in their health and associated changes in sexual behavior and fertility desires. As more women access

ART, the fertility of HIV-positive women who are not yet on ART also increases due to the selective removal (onto ART) of those formerly at more advanced stages of infection. These two trends contribute to similar age-specific fertility rates among women on ART and not yet on ART, although their fertility remains below that of HIV-negative women. The relative stability of age-specific fertility among HIV-positive women over time may reflect the counterbalancing effects of increased fertility of HIV-positive women due to ART and secular declines in fertility (13).

Returning to the principal motivation for this study – an urgent need to inform estimates for HIV service provision and the monitoring of HIV prevalence, we draw the following tentative conclusions: First, HIV-positive pregnant women will comprise a growing proportion of the ANC population in the near future due to reductions in the fertility differential between HIV-positive and HIV-negative women, and the longer survival of HIV infected women. The implication is that apparent increases in HIV prevalence among pregnant women may reflect changes in the fertility differential, as well as reflecting the underlying population-wide HIV trends. Failing to account for narrowing of the fertility rate ratio between HIV-positive and HIV-negative women could result in over-estimates of population HIV increases derived from prevalence among pregnant women. Second, although reductions in the fertility differential will increase the need for PMTCT services, more of these women will conceive while on ART, reducing the risks of onward transmission to their children.

Notably, the data in the reviewed published papers are concentrated over a period in which ART was rapidly expanding (2005-2010) but not as well established as today. Changes in the characteristics of women initiating ART and the widening of CD4 guidelines suggest that we should be cautious about extrapolating data from 2005-2010 to the current or a future situation. The recent rapid adoption of the Option B+ policy, which recommends lifelong ART to all HIV-positive pregnant women, and WHO's recommended policy of universal eligibility for ART (30), will mean that women initiate ART at earlier stages of their disease, before an advanced infection affects their fecundity. As this trend continues, the fertility of HIV-positive women on ART may approach that of HIV-negative women.

Given these recent and rapid changes in ART policy and availability, there is an urgent need to analyse data from the post-2010 period. Fortunately, researchers seem aware of this need—7 of the 18 studies in this review were published in 2015 or the first few months of 2016, including the only three population-based studies.

Future research on the impact of ART on fertility of women

The studies included in the systematic review came largely from HIV clinics. Given the limitations of HIV clinic data, which lack an HIV-negative comparison and are limited to the subset of HIV positive women engaged in care, other data sources such as ANC clinics, general population cohort studies (e.g. demographic surveillance sites), and retrospective population-based surveys (e.g. DHS and the new Population-based HIV Impact Assessment surveys (PHIA)(31)) are likely to be the most informative in the future. Nonetheless, interpretation of currently available data from each of these sources is difficult because reporting of ART utilization and the timing of ART initiation relative to pregnancy incidence tend to be less precise if self-reported. Precision about this is important considering the high risk of potential confounding: many women are diagnosed and initiate ART *because* they are pregnant, particularly under Option B+, and the unique PMTCT needs of women on- and not-on-ART in the first trimester. In all of these data sources, retrospective reporting may be enhanced by inclusion of a specific survey question about whether the women was on ART *prior* to the first ANC visit, in addition to the now standard questions about HIV testing and PMTCT provision during the pregnancy.

Among these data sources, ANC clinic data are less useful. Although they include data about both HIV-positive and HIV-negative women, the denominator for each group is unknown. An assumption about the population size and prevalence in the catchment population is required to calculate relative fertility rates. Moreover, to date, routine ANC clinic reporting has not tended to include reporting of whether women were already on ART, nor age stratification.

Prospective general population cohorts may be considered the gold standard if they also precisely identify the timing of ART relative to pregnancy through prospective linkage to HIV service delivery data. However, these data are only available in a few eastern and southern African countries, and tend to be among rural populations. DHSs, PHIA and similar nationally representative surveys with retrospective fertility histories potentially overcome this limitation: they include both urban and rural populations and will cover a large number of SSA countries. These surveys will increasingly include biomarker measurement of antiretroviral use, but inclusion of a specific question about whether ART was initiated prior to pregnancy is essential. Estimates from retrospective fertility histories, however, are susceptible to survivorship bias in which fertility experiences of recently deceased women are excluded, although survivorship bias may be less important in the ART era than earlier when HIV mortality was higher. They are also susceptible to the underreporting of early infant mortality, which will disproportionately affect HIV-positive women not on ART and could artificially inflate estimates of the effect of ART on fertility as declines in early infant mortality could ap-

pear as increases in fertility.

This review focused on fertility differentials between women on ART and comparison populations as a critical first step in understanding how ART use affects fertility. Future studies, however, should be sensitive to the relative impact of biological versus behavioral differences—volitional and not—in the fertility response to ART in different settings, as they will provide essential inputs for models such as Spectrum (32, 33) that attempt to estimate the future direction of HIV and the family planning needs—including safe conception counseling—of these women.

Conclusion

Current evidence indicates that fertility increases after the first year on ART, but remains lower than in HIV-negative women of the same age. These conclusions, however, are based on data largely from 2005-2010 when ART was scaled up. Caution should be exercised generalizing to the current era when guidelines have changed, women start ART earlier, coverage is higher, and women have been on ART longer. Improving evidence about fertility among women on ART is an urgent priority for planning HIV resource needs and understanding HIV epidemic trends.

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Table 1 Studies examining the relative fertility of HIV positive women in sub-Saharan Africa during the era of ART

Authors (Year)	Setting	Period	Sample	Design	Comparison	Outcome	Key findings	Limitations for understanding ART-fertility relationship
Gregson <i>et al.</i> (2015)	rural Zimbabwe 12 communities	2009-2011	1,333 HIV+ women (29% on ART); 6078 HIV- women	Cross-sectional analysis of prospective cohort	On-ART : pre-ART HIV+ : HIV-	Pregnancy prevalence	HIV+ women ≥ 25 have lower fertility than HIV- women. Degree and age pattern of reduced fertility similar on and off ART. Differences in fertility by HIV status remain substantial at older ages.	Unclear when women initiated ART relative to index pregnancy and exposure time. Self-reported pregnancy and ART use.
Marston <i>et al.</i> (2016)	Tanzania, Uganda, South Africa 4 community cohorts	2002-2011	59,440 HIV+ and HIV- women	Prospective cohorts	HIV+ : HIV- Over time periods	Age-specific fertility rates	Narrowing of the fertility deficit between HIV+ and HIV- women between the pre-ART and post-ART periods. Largely due to reductions in the fertility of HIV- women. Age-specific fertility of HIV+ women still lower than HIV- women at all ages but 15-19.	No measurement of individual ART use within sample. Self-reported births (may undercount early infant deaths).
Souza and Moultrie (2015)	Malawi nationally-representative data	2004-2010	1,207 HIV+ women; 7680 HIV- women	Repeated cross-sectional	HIV+ : HIV- Over time periods	Fertility rate and probability of birth in last year	The probability of giving birth for HIV+ women relative to HIV- women increased between 2004 and 2010.	No measurement of individual ART use within sample. Self-reported births (may undercount early infant deaths). Some uncertainty around timing of pregnancy relative to seroconversion.
Myer <i>et al.</i> (2010)	urban Rwanda, South Africa, Zambia, Cote d'Ivoire, and Kenya 11 HIV clinics	2003-2007	4,531 recently post-partum HIV+ women	Retrospective cohort	On-ART : pre-ART	Pregnancy incidence	Pregnancy rate was higher among women on ART than pre-ART. Pattern consistent across countries though not always strong and statistically significant.	Enrollment limited to post-partum (and thus parous) women. Exclude women who got sterilized after index pregnancy ^a . Self-reported pregnancy. Women who start ART midway through study move into ART group. Although this a strength in some ways, it may also inflate estimates relative to pre-ART group who are by definition immediately post-partum.

Elul <i>et al.</i> (2016)	Kenya and Uganda 26 HIV clinics	2001-2009	47,313 HIV+ women (61% initiating ART)	Retrospective cohort	On ART; pre-ART	Pregnancy incidence	No difference in pregnancy incidence among women on ART and pre-ART in adjusted analyses. Results adjusted for time-varying CD4 count. Women on ART and pregnant at enrollment had subsequent pregnancy more quickly than women not on ART and not pregnant at enrollment.	Age treated as linear variable. Self-reported pregnancy.
Patel <i>et al.</i> (2015)	Kenya 19 HIV clinics	2011-2013	24,560 HIV+ women (68% on ART at baseline)	Retrospective cohort	On ART; pre-ART	Pregnancy incidence	Pregnancy incidence did not differ among women using a nevirapine-based ART regimen compared to no-ART. Results adjusted for time-varying CD4 count.	Age treated as linear variable. Self-reported pregnancy.
Guthrie <i>et al.</i> (2011)	urban Kenya HIV clinic (enrolled at VCT)	2007-2010	279 HIV+ women in sero-discordant relationships	Prospective cohort	On-ART : pre-ART	Pregnancy incidence	Pregnancy rate fell following ART initiation. Difference was of similar magnitude but no longer statistically significant after adjusting for age and baseline CD4 count.	Small sample size. Pregnancy analysis was a secondary analysis of the paper and insufficient details are provided.
Makumbi <i>et al.</i> (2011)	rural Uganda Community-based HIV care program	Unclear (post-2004)	956 HIV+ women (26% on ART)	Prospective cohort	On-ART : pre-ART	Pregnancy incidence	Pregnancy rate was almost twice as high among women on ART. Pregnancy rate was highest in women with good immunologic response to treatment.	Follow respondents more closely after initiate ART, so more likely to identify on-ART pregnancies. Analyses were run separately for women pre-ART and on-ART. Compare overall rates across groups but without adjusting for age differences of populations. Excluded women not at risk of pregnancy including those using Depo or Norplant [®] .
Maier <i>et al.</i> (2009)	semi-urban Uganda HIV clinic	2005-2006	501 HIV+ women (45% on ART)	Cross-sectional	On-ART : pre-ART	Live birth and pregnancy in previous 3 years	Fewer recent births among women on ART but higher fertility desires.	No control for length of time on ART. Less precise accounting of ART status at time of conception. Self-reported birth and pregnancy data.

Asiimwe-Kateera <i>et al.</i> (2015)	urban Rwanda HIV clinic	2007-2010	312 HIV+ women (36% newly on ART)	Prospective cohort	On-ART : pre-ART	Pregnancy incidence	Pregnancy incidence was not statistically different between women on-ART and pre-ART.	Small sample size. Analyses are not adjusted for age and other sociodemographic differences despite a 7 year difference in median age between pre- and on-ART women.
Lancaster <i>et al.</i> (2015)	Uganda and Zimbabwe Clinical study on HIV genital shedding and disease progression	2001-2009	306 newly infected HIV+ women	Prospective cohort	On-ART : pre-ART	Pregnancy incidence	Pregnancy incidence higher among ART-naïve women than women on ART (unadjusted).	Small sample of on-ART women. Analyses are not adjusted for age or other differences between groups.
Kabami <i>et al.</i> (2014)	rural Uganda HIV clinic	2006-2010	3,144 HIV+ women (41% on ART)	Retrospective cohort	On-ART : pre-ART Over time periods	Pregnancy incidence	Pregnancy rate increased among HIV+ clinic population over time. No difference by ART use (unadjusted). Larger improvements in CD4 were associated with lower risk of pregnancy (may indicate lower CD4 starting point).	Analyses are not adjusted for age or other differences between groups.
Tweya <i>et al.</i> (2013)	urban Malawi ART clinic	2007-2010	4,738 HIV+ women	Retrospective cohort	Time on ART Indirectly HIV+ on ART : general population	Pregnancy incidence	Pregnancy rate was low in first 6 months on ART. After 6 months, women had similar age-specific pregnancy rates to general urban Malawian population. Pregnancy rate lower among women who initiated at WHO stage 3/4 compared to WHO stage 1/2 with CD4 count eligibility.	Self-reported pregnancy.
Schwartz <i>et al.</i> (2012)	urban South Africa 4 ART clinics	2009-2011	822 HIV+ women on ART	Prospective cohort	Time on ART	Pregnancy incidence	No significant differences in pregnancy rates by time on ART.	Exclude sexually inactive women and women with sterilizations ^a . Age treated as linear variable. No HIV- or ART naïve comparator.

Homsy <i>et al.</i> (2009)	rural Uganda Home-based care program	2003-2006	733 HIV+ women initiating ART	Prospective cohort	Time on ART Indirectly HIV+ on ART : HIV- general population	Pregnancy incidence	Pregnancy rate increased with time on ART, peaking 1-year after initiation. Peak pregnancy rate of women on ART still below 2007 national estimate for 35-39 age group.	Older and higher parity sample. Age treated as linear variable.
Kaida <i>et al.</i> (2013)	rural Uganda ART clinic	2005-2011	351 HIV+ women initiating ART	Prospective cohort	Time on ART	Pregnancy incidence	Pregnancy rate changed with time since ART initiation: highest 6-12 months after and then declined until 4 years post-initiation (due to second pregnancies after birth interval).	Small sample size. Self-reported pregnancy. Censor women at sterilization ^a . Age treated as continuous variable (but age range only 27-37 so may not be problematic).
Burgos-Soto <i>et al.</i> (2014)	Burkina Faso, Benin, Cote d'Ivoire, Gambia, Guinea-Bissau, Mali, Nigeria, and Senegal 15 ART clinics	1998-2011	29,425 HIV+ women from time of ART initiation	Retrospective cohort	Time on ART Over time periods	Pregnancy incidence	Pregnancy incidence of women on ART increased over time (2007-2011 vs pre-2005). Pregnancy incidence was highest in women who initiated ART at WHO Stage 1/2 compared to 3/4. Pregnancy incidence peaked at year 4 (not adjusted for age).	No HIV- or ART naïve comparator. Some analyses are not adjusted for age. Self-reported pregnancy. No HIV- or ART naïve comparator.
Westreich <i>et al.</i> (2012)	urban South Africa ART clinic	2004-2009	5,996 HIV+ women from time of ART initiation	Retrospective cohort	On ART by time-varying CD4 count and adherence	Pregnancy incidence	Poor ART adherence (<80%) associated with lower pregnancy incidence (unadjusted). CD4<100 associated with reduced rate (unadjusted).	Authors present cumulative incidence for many analyses, excluding repeated pregnancies. No HIV- or ART naïve comparator.

^a This potentially introduces a bias for understanding the effect of ART on fertility at a population level, particularly to the extent that contraceptive choices or abstinence may be the result of one's HIV status or ART use.

Figure 1 Search process for selection of studies