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The effects of HIV on fertility by infection duration: evidence from African population cohorts before antiretroviral treatment availability

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Objectives: To estimate the relationship between HIV natural history and fertility by duration of infection in east and southern Africa before the availability of antiretroviral therapy and assess potential biases in estimates of age-specific subfertility when using retrospective birth histories in cross-sectional studies.

Design: Pooled analysis of prospective population-based HIV cohort studies in Masaka (Uganda), Kisesa (Tanzania) and Manicaland (Zimbabwe).

Methods: Women aged 15–49 years who had ever tested for HIV were included. Analyses were censored at antiretroviral treatment roll-out. Fertility rate ratios were calculated to see the relationship of duration of HIV infection on fertility, adjusting for background characteristics. Survivorship and misclassification biases on age-specific subfertility estimates from cross-sectional surveys were estimated by reclassifying person-time from the cohort data to simulate cross-sectional surveys and comparing fertility rate ratios with true cohort results.

Results: HIV-negative and HIV-positive women contributed 15 440 births and 86 320 person-years; and 1236 births and 11 240 000 person-years, respectively, to the final dataset. Adjusting for age, study site and calendar year, each additional year since HIV seroconversion was associated with a 0.02 (95% confidence interval 0.01–0.03) relative decrease in fertility for HIV-positive women. Survivorship and misclassification biases in simulated retrospective birth histories resulted in modest underestimates of subfertility by 2–5% for age groups 20–39 years.

Conclusion: Longer duration of infection is associated with greater relative fertility reduction for HIV-positive women. This should be considered when creating estimates for HIV prevalence among pregnant women and prevention of mother-to-child transmission need over the course of the HIV epidemic and antiretroviral treatment scale up.

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Introduction

The effects of HIV infection on fertility have been extensively studied in generalized HIV epidemic settings in sub-Saharan Africa [1–6]. This was of interest for two reasons: first, to forecast the demographic impacts of hyperendemic HIV [7,8] and, second, because HIV prevalence among pregnant women was widely used for estimating general population HIV prevalence levels and trends [9–11]. More recently, the need to plan and evaluate prevention of mother-to-child transmission (PMTCT) programmes has further increased the importance of accurate predictions of fertility of HIV-positive women and changes therein.

Existing literature, largely based on analysis of cross-sectional data, has demonstrated that the relationship between HIV infection and fertility depends strongly on age. Among young women (age 15–19 years) antenatal care prevalence is higher than general population prevalence because both pregnancy and HIV risk occur among the subset of women who are sexually active, but among older age groups the fertility rate ratio (FRR) among HIV-positive women becomes increasingly lower relative to HIV-negative women [1,12,13].

Currently, the Spectrum model (Avenir Health, Connecticut, USA) uses estimates of the FRR for HIV-positive to HIV-negative women by age-group estimated by Chen and Walker [1] to generate estimates of HIV prevalence among pregnant women and need for PMTCT. However, rather than a direct effect of age, the lower prevalence among older pregnant women may primarily be associated with reduced fertility during later stages of HIV infection [5,14–17]. This distinction is potentially important because of its interaction with the stages of the HIV epidemic – during the early exponential growth period of the epidemic, many more women are recently infected, and so HIV-related subfertility will be lower than later in the epidemic, even among older women. Moreover, antiretroviral treatment (ART) is disproportionately provided to those infected the longest and experiencing the most serious clinical symptoms – those who are expected to experience the greatest fertility reductions. If the effects of HIV on fertility are strongly related to the duration of infection, then these two effects may contribute to biased predictions about need for PMTCT services as ART programmes scale up.

Finally, the hypothesized relationship between duration of HIV infection and fertility may influence our ability to estimate the relationship between HIV and fertility. Widely used estimates of age-specific FRRs by HIV status rely on cross-sectional Demographic and Health Survey data to compare fertility over the previous 3 years among HIV-positive and HIV-negative women [1]. This poses two potential biases (Fig. 1). First, it excludes women who do not survive the 3-year period preceding the survey. If duration of infection influences fertility, then this survivorship bias would exclude women with the lowest fertility, resulting in an underestimate of subfertility based on cross-sectional surveys. Second, retrospective analyses assume that the HIV status at the time of the survey is unchanged over the previous 3 years. For women who seroconverted during the 3 years prior to the survey, this misclassifies some HIV-negative person-time as HIV-positive, again potentially overestimating the true fertility of HIV-positive women.

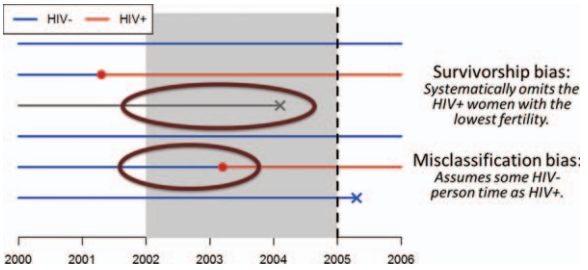

Fig. 1. Survivorship and misclassification bias.

In this analysis, we estimate the relationship between the imputed duration of HIV infection and fertility using data from three prospective general population open cohorts in Uganda, Tanzania and Zimbabwe – all members of the ALPHA network (London School of Hygiene & Tropical Medicine, London, UK) [18]. The objective of this analysis is to estimate the relationship of HIV natural history and fertility in the absence of treatment, and as such we censor the cohort data at the time when ART became available in the population (population-wide fertility trends in these cohorts since ART scale up have been described elsewhere [19]). We use the prospective demographic and HIV surveillance data to empirically quantify the expected magnitude of survivorship and misclassification biases on age-specific subfertility from cross-sectional surveys.

Methods

Sites and setting

Data come from three community-based demographic and HIV open-cohort studies. Kisesa (managed by the National Institute for Medical Research Mwanza) located in northwestern Tanzania, was established in 1994 and has a population of around 34 000. It is predominately rural with a small trading centre on the main road. The average HIV prevalence between 1994 and 2010 was 6% [20]. The Manicaland study (managed by the Biomedical Research and Training Institute and Imperial College London) in Zimbabwe was established in 1998. A prospective household census (population size approximately 37 000) and general population cohort survey (10 000–12 000) were initiated in 12 geographically distinct study sites spread across three districts, with follow-up rounds conducted every 2 or 3 years. The Manicaland study sites comprise two small towns, four

agricultural estates, two roadside settlements and four subsistence farming areas. Overall adult HIV prevalence was around 25% in the late 1990s and has declined steadily to around 15% in 2012–2013 [21]. Masaka (managed by MRC/UVRI Uganda Research Unit on AIDS) is situated in rural southwest Uganda and was established in 1989. Its initial population was around 10 000 which then increased to 18 000 when 10 villages were added to the census area in 2000. Average HIV prevalence between 1989 and 2011 was 8% [22].

Fertility data

In Kisesa, there are two sources of data that are used to estimate fertility. At each demographic surveillance round conducted one to two times per year, a proxy respondent is asked whether each woman in the household gave birth since the previous round and the birth outcome. Also, all new members of the household, including newborns, are linked to their mother if she lives in the household. These two pieces of information are reconciled to give the date of delivery of each birth observed in the demographic surveillance site.

In Masaka, there are four sources of data for estimating fertility. At each annual census, women of child-bearing age are asked whether they were pregnant in the previous 12 months and the birth outcome. The names and identification number of the child are recorded on the mother's record. Second, each new member of the household is enumerated during the annual census and the reasons for joining obtained. If the reason is new born, the mother's identification number is recorded on the child's census record. Third, village leaders are asked to report all births in their village on a monthly basis to the study clerks. This information is entered, and any child reported by these recorders but not on census is added to the census file. Fourth, every 3 years, all children aged less than 18 years are asked about their parents to establish/confirm who they are and their vital status.

In the Manicaland study, survey rounds are conducted every 2–3 years. At each survey round, eligible women are enumerated in a household census and invited to participate in an open-cohort study. Participants report all births since the previous survey round through a structured questionnaire. For women who die between survey rounds, any births occurring since the previous survey round are recorded in a verbal autopsy interview with the next of kin.

HIV data

In Kisesa, the HIV surveys were carried out separately to the demographic surveillance rounds every 2–3 years, and data were linked afterwards using unique personal identifiers. In Masaka, HIV testing was done immediately after demographic surveillance rounds that were used to list those eligible for HIV testing. HIV testing took place in the home for all sites apart from Kisesa where temporary village clinics are used, to which people are transported from their homes. Prior to the availability of antiretroviral therapy, testing protocols used informed consent without disclosure, so that participants did not learn the results of the HIV research tests. In Manicaland, following household census enumeration, research assistants interview eligible individual participants to collect dried blood spot samples, which are transported to and analysed in an offsite laboratory.

Statistical analysis

Imputation of date of seroconversion

Calculating the fertility rate by duration of HIV infection requires data about when a woman seroconverted, which is not exactly observed. We generated 100 imputations for the date of seroconversion for each HIV-positive woman. For women who are observed HIV-negative in one survey round and HIV-positive in a subsequent round (seroconverters), we imputed dates of seroconversion from a uniform distribution between the dates of the last negative and first HIV-positive test.

For women who were already HIV positive the first time they were tested in the cohort (prevalent cases), we imputed 100 seroconversion dates from a distribution determined by the convolution of the age-specific HIV incidence rates and the probability of surviving from seroconversion until the woman's latest age at interview.

Fertility rate ratio by duration of infection

Person-time and live births of women of reproductive age (15–49 years) who had ever tested for HIV in the studies were eligible for inclusion in the analysis. HIV-negative person-time for women with no subsequent positive test was assumed to last for up to 5 years past their last negative test, the exact cut-off point was determined by the HIV incidence rates in the sites, defined as the time at which the cumulated probability of becoming infected following the last negative test reached 5%. Data for each cohort were censored at the start of ART introduction (Kisesa March 2005, Masaka January 2004 and Manicaland June 2005) to estimate the intrinsic relationship between HIV and fertility before the availability of antiretroviral therapy. For women ever testing HIV positive, imputed seroconversion dates were used to assign person-time by HIV status.

The imputed duration of infection is defined as 0 for HIV-negative and is treated as a continuous variable in years following seroconversion. FRRs by HIV status and duration of infection are calculated using piecewise exponential regression allowing for clustering of births in each women, adjusting for age-specific fertility in each site and a log-linear trend in fertility over calendar time centred on the year 2001. The analysis was repeated 100 times using independently imputed seroconversion dates. The log of the hazard rate ratios from the imputations were

combined using Rubin's rules [23] to give confidence intervals (CIs) that reflect the uncertainty about the exact date of seroconversion. Older age at infection pre-ART is associated with a shorter survival time [24] independent of current age [25]. We investigated whether this could also have an effect on subfertility classified by duration of infection (model not shown).

The effects of survivorship and misclassification bias in retrospective survey analysis

We quantified the potential magnitude of survivorship and misclassification biases when estimating age-specific subfertility from cross-sectional surveys by using the population cohort data to simulate the 3-year retrospective fertility history analysis and compared the resulting age-specific FRRs with the true FRRs observed in the cohorts. Person-time was classified in 3-year intervals 2000–2002 and 2003–2005 then aggregated over the 6-year period. We calculated actual subfertility by age (adjusted for study site, residence and calendar time), then calculated subfertility by age as assumed in cross-sectional studies by allocating all the person-time of women who were positive at the end of the time period to HIV positive for the whole period (simulating misclassification) and removing any person-time and births to women who died in the period (simulating survivorship bias).

All analysis was done using Stata 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Ethics statement

Each of the three sites contributing data to the pooled analysis received ethical clearance from the appropriate local ethics review bodies and from the corresponding Institutional Review Boards at relevant collaborating partner universities.

Results

Estimates of HIV subfertility by duration of infection

The dataset compiled for women aged 15–49 years contained 15 451 births and 86 280 person-years to HIV-negative women, 993 births and 9580 person-years to HIV-positive women and 315 births and 2510 person-years with HIV status unknown. Prior to imputation, the latter group comprised the time before a first positive test and person-time in the seroconversion interval (Table 1). Kisesa contributed the most births (54%) and person-years (42%) (Table 1). Manicaland contributed the highest number of births and person-years to HIV-positive women (477 births, 5750 person-years) due to the higher HIV prevalence in Zimbabwe. After imputation of seroconversion dates, HIV-negative and HIV-positive women contributed 15 440 births and 86 320 person–years, and 1236 births and 11 240 person-years, respectively. The total fertility rate over the pre-ART time period used was highest in Kisesa at 6.2 followed by Masaka at 5.2 and lowest in Manicaland at 3.1.

Crude fertility rates patterns were broadly similar in the observed prevalent positive person-time compared with the imputed positive person-time with the rates slightly higher in the imputed positive person-time, consistent with imputed positive being biased towards earlier duration after seroconversion (not shown). Crude rates show a decrease in fertility by duration of infection (Table 2).

Compared with HIV-negative women, the relative fertility of HIV-positive 20–24-year-olds was 0.72 (95% CI 0.66–0.79), and relative fertility further reduced with age (Table 3, Model 1). The 15–19-year-old HIV-positive women have higher fertility compared with those who are uninfected due to the fact that many women in this age group are not sexually active and therefore are not exposed to HIV.

Including duration of infection in the model showed that each additional year since seroconversion was associated with a 0.979 (95% CI 0.965–0.995) times reduction in fertility for HIV-positive women, adjusted for age, the effect of age at seroconversion, study site and calendar year (Model 2, Table 3). Accounting for duration attenuated the relative fertility of positive women compared with negative women to 0.78 (95% CI 0.70–0.88) and similarly for other age groups (Model 2, Table 3).

Restricting the model to HIV-positive women (not shown) shows that with increasing year of age at seroconversion, there is an increase in the effect of duration on subfertility (FFR 0.997, 95% CI 0.994–0.999).

Table 1. Births and person-years by HIV status and study site for women aged 15–49 years who ever tested for HIV.

	Kisesa		Manicaland		Masaka		All sites	
HIV status	Births	Person-years per 1000	Births	Person-years per 1000	Births	Person-years per 1000	Births	Person-years per 1000
Negative	8581	38.11	2003	19.87	4867	28.30	15 451	86.28
Positive	284	2.17	381	4.93	328	2.48	993	9.58
Unknown	162	1.12	96	0.85	57	0.54	315	2.51

Note for those HIV-negative women were included up to 5 years after last negative test.

Table 2. Crude rates with imputed data by HIV status.

	HIV negative			Imputed positive			All imputed data		
	Births	Person-years per 1000	Fertility rate per 1000	Births	Person-years per 1000	Fertility rate per 1000	Births	Person-years per 1000	Fertility rate per 1000
Age Group									
15–19	2683	21.98	122.07	122	0.70	173.47	2806	22.69	123.66
20–24	4446	15.40	288.66	381	1.97	193.19	4826	17.37	277.83
25–29	3505	12.83	273.12	393	2.69	146.36	3898	15.52	251.18
30–34	2486	11.03	225.41	209	2.29	91.31	2694	13.31	202.35
35–39	1592	9.72	163.76	106	1.66	63.72	1698	11.39	149.14
40–44	621	8.53	72.87	21	1.25	16.53	642	9.78	65.66
45–49	107	6.83	15.66	4	0.67	6.11	111	7.50	14.80
HIV status									
Negative	15440	86.32	178.87				15440	86.32	178.87
Positive				1236	11.24	109.98	1236	11.24	109.98
Duration of infection									
1 year				130	0.81	160.13	130	0.81	160.13
1–2 years				265	1.87	142.15	265	1.87	142.15
3–4 years				252	1.87	135.13	252	1.87	135.13
5–6 years				205	1.68	121.66	205	1.68	121.66
7–8 years				145	1.39	104.62	145	1.39	104.62
9+ years				226	3.56	63.52	226	3.56	63.52
Study Site									
Kisesa	8582	38.16	224.89	389	2.78	139.75	8971	40.94	219.10
Manicaland	2009	19.89	100.67	477	5.75	82.97	2480	25.65	96.70
Masaka	4855	28.26	171.78	370	2.70	136.78	5224	30.96	168.73
Calendar Year									
1990	186	1.08	171.57	20	0.13	148.61	206	1.22	169.06
1991	336	1.61	209.15	34	0.19	179.94	370	1.80	206.05
1992	322	1.66	193.84	34	0.18	184.99	356	1.85	192.97
1993	232	1.68	138.42	36	0.18	197.64	268	1.86	144.22
1994	587	2.98	197.17	44	0.27	164.69	631	3.25	194.48
1995	1109	4.93	225.06	60	0.40	151.54	1170	5.33	219.56
1996	1080	5.02	214.92	61	0.41	149.27	1141	5.43	210.00
1997	1111	5.11	217.29	65	0.43	152.19	1176	5.54	212.30
1998	919	5.16	178.27	37	0.42	88.61	956	5.57	171.58
1999	1369	7.02	195.03	104	0.96	107.58	1473	7.98	184.49
2000	1562	9.17	170.37	155	1.48	104.97	1718	10.65	161.28
2001	1684	9.72	173.25	145	1.46	99.67	1829	11.18	163.65
2002	1711	10.23	167.27	169	1.49	113.05	1881	11.73	160.37
2003	1750	10.97	159.58	130	1.56	82.92	1880	12.53	150.02
2004	1242	7.92	156.90	108	1.26	86.04	1351	9.18	147.16
2005	237	2.06	115.13	34	0.42	81.86	271	2.48	109.51

Births and person-years are averaged over 100 datasets.

Estimates of survivorship bias in retrospective surveys

Age-specific subfertility was larger in the ALPHA sites compared with that found by Chen and Walker [1] apart from the 15–19-year age group (Fig. 2a). The reduction in fertility was 3–12% greater in the age groups 20–34 years and somewhat larger at the oldest age groups, for example 41% lower in the 40–44-year age group. However, CIs encompassed Chen and Walker estimates apart from the 40–44-year-old age group. Figure 2a compares the observed subfertility by age in the cohorts (red dots) with the subfertility estimates when analysed using the assumptions of a retrospective cross-sectional survey (blue triangles). Estimates with simulated misclassification and survivorship bias attenuated the subfertility by age by between 2 and 5% in the age groups between 20 and 39 years and 22% in the 40–44-year age group.

There was some evidence for variation of age-specific subfertility by study site with subfertility in Manicaland lower than in Masaka and Kisesa (Fig. 2b).

Discussion

These data show that longer duration of HIV infection is associated with increased subfertility. Estimating age-specific HIV subfertility using retrospective cross-sectional surveys underestimates subfertility, particularly for older ages, due to survivorship bias being more important at longer duration of infection, which corresponds to greater fertility-reducing effects of HIV infection.

Many studies have documented the effect of HIV on fertility and on age-specific subfertility [1,4,12,13] at the

Table 3. Effects of HIV on fertility by age and duration of infection.

	Model 1 – no duration		Model 2 – with duration	
	FRR	95% CI	FRR	95% CI
Duration of infection			0.979	(0.964–0.995)
HIV status				
HIV negative	1		1	
HIV positive	0.72	(0.66–0.79)	0.78	(0.70–0.88)
Effects of HIV by age				
15–19, HIV positive	2.02	(1.67–2.45)	1.95	(1.60–2.38)
20–24, HIV positive	1		1	
25–29, HIV positive	0.86	(0.75–0.98)	0.90	(0.78–1.03)
30–34, HIV positive	0.69	(0.58–0.81)	0.74	(0.62–0.89)
35–39, HIV positive	0.73	(0.58–0.92)	0.81	(0.63–1.03)
40–44, HIV positive	0.46	(0.28–0.76)	0.52	(0.32–0.87)
45–49, HIV positive	0.90	(0.27–2.99)	1.01	(0.30–3.39)
Age group				
15–19	0.50	(0.47–0.54)	0.50	(0.47–0.54)
20–24	1		1	
25–29	0.96	(0.92–1.01)	0.96	(0.92–1.01)
30–34	0.81	(0.77–0.85)	0.81	(0.77–0.85)
35–39	0.63	(0.59–0.67)	0.63	(0.59–0.67)
40–44	0.31	(0.28–0.35)	0.31	(0.28–0.35)
45–49	0.09	(0.07–0.12)	0.09	(0.07–0.12)
Study site				
Kisesa	1		1	
Manicaland	0.66	(0.62–0.71)	0.67	(0.62–0.71)
Masaka	0.87	(0.82–0.92)	0.87	(0.82–0.92)
Calendar year	0.99	(0.99–1.00)	0.99	(0.99–1.00)

Results from exponential regression of fertility rates as a function of HIV status, age and duration of infection controlling for interaction between study site and age (not shown), study site and calendar year (not shown). Calendar year is centred at 2001, age at seroconversion is centred at age 25. Pooled results based on 100 datasets for imputed date of seroconversion. CI, confidence interval; FRR, fertility rate ratio.

population level during the pre-ART period. A number of studies in sub-Saharan Africa have looked at disease progression in relation to fertility, a case–control study in Uganda found that high viral load was associated with reduced rates of pregnancy and a reduction in live births [5], despite being sexually active and not using contraception. Also, a clinical cohort found that fertility is reduced from the earliest stage of HIV infection with a large reduction in fertility following the progression to AIDS [16] – this finding was adjusted for sexual activity but not for contraceptive use. A clinical cohort study in Tanzania also found reduced fertility related to clinical stage of HIV [17] adjusting for social and demographic characteristics. A multisite HIV care and treatment programme analysis showed a strong association between disease progression and a reduction in the incidence of pregnancy [15].

Increased subfertility by duration of infection at the population level could have both biological and behavioural factors. Biologically, as well as increases in viral load or decreases in $CD4^+$ cell count as explanatory factors, the semen quality of HIV-positive partners could be reduced over the time of their infection [26–28] or their increased illness could impact on their sexual activity. In terms of behaviour, HIV-positive women are more likely to be widowed [6,29,30] due to having had an HIV-positive partner. Although voluntary testing and counselling was rare in these sites prior to ART introduction, suspicion of HIV status or illness in a partner with HIV may reduce the desire for more pregnancies [31], which may be more obvious at longer durations of infection and it may also increase divorce or separation [6,30].

Increased age at seroconversion accelerated the effects of infection duration on subfertility. Older age at infection leads to shorter survival postinfection [24,25], so a shorter duration to low $CD4^+$ cell count and higher viral load have been shown to reduce fertility. Also, at older ages of seroconversion, it is more likely that the partner (who is more likely to be older) has been infected for a longer duration; therefore, there is a higher chance of widowhood early on in the women's HIV infection lowering her changes of pregnancy. Finally, older women are likely to have higher parity and therefore may have lower desires for more children than a younger woman who has none or few children.

Compared with the demographic and health survey (DHS) analysis by Chen and Walker [1], ALPHA cohorts showed greater fertility reductions among HIV-positive women by 5-year age group, particularly in the older age groups. Around half of this discrepancy was explained by biases inherent in estimating subfertility from cross-sectional data due to not including the person-years and births of those who died prior to interview and classifying all person-years according to the HIV status at time of interview.

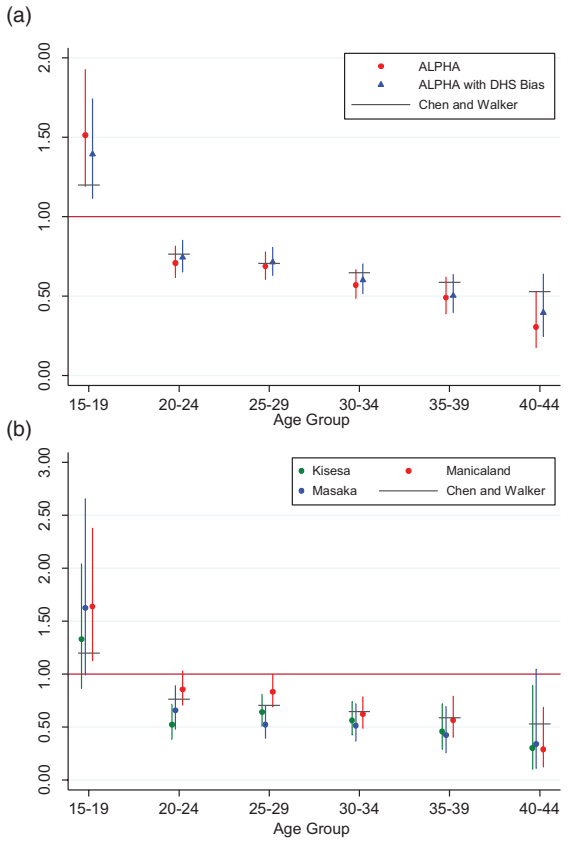

Fig. 2. (a) Fertility rate ratio from Chen and Walker – survivorship bias (b) age-specific fertility rate ratio (HIV positive/HIV negative) by study site compared with Chen and Walker.

Residual differences between our findings and those of Chen and Walker [1] could have a number of causes. This DHS analysis uses countries across south, east and western Africa, whereas our analysis uses study sites from east and southern Africa where Manicaland, Zimbabwe showed lower subfertility than the two east Africa sites (although CIs overlapped), which may indicate some differences in subfertility and duration of infection in different settings as found in previous studies [3,6]. Modern contraceptive use by all women is much higher in Zimbabwe at 40.1% in 2005–2006 compared with Tanzania and Uganda, 22.5% in 2004–2005 and 19.6% in 2006, respectively [32], which may contribute to these differences [6]. Deliveries and the deaths of children dying in early infancy (particularly in the neonatal period) could be underreported in the ALPHA studies due to recall bias or lack of knowledge on the part of a proxy respondent, which would affect HIV-positive women disproportionally due to the high infant mortality of children infected through vertical transmission [33]. This could artificially increase subfertility estimates in the cohort studies. The DHS will be prone to more recall bias than the cohort studies; however, if analysis is limited to the first few years prior to the interview and the respondent is the women rather than a proxy, it is possible that this will lead to less bias in reporting of births to infants who have died in DHS compared with ALPHA studies. We find that subfertility increases with duration of HIV infection in the absence of ART. This has two important implications that should be considered in future HIV epidemic estimates and the estimates of need for PMTCT. First, over the course of the epidemic, the distribution of duration of infection changes. During the exponential growth phase, a higher proportion of women will be recently infected, and as incidence declines average duration of infection will become longer. This means that the population-level effects of HIV on fertility, and hence the relationship between HIV prevalence measured among pregnant women and general population prevalence, will change.

Second, initiation of antiretroviral treatment has been disproportionately among women in later stages of infection who might be expected to have the lowest fertility rates. Thus, following ART scale up, not only might women on ART have increased fertility [34], but also the fertility of untreated HIV-positive women may be higher because those who would have the lowest fertility are selectively removed into the treatment group. Implementation of Option B+ over the past several years, in which all pregnant women are initiated on lifelong ART, will further change these dynamics. In light of the demonstrated association between duration of infection and fertility reduction, we recommend that model-based approaches account for not only age but also stage of infection and ART status when estimating HIV prevalence among pregnant women and PMTCT need.

Our results also imply that there are differences in fertility by setting. This underscores that, where possible, locally available data such as prevalence from routine HIV testing of pregnant women should be used in place of default model values to inform appropriate model assumptions about subfertility when generating estimates of PMTCT need.

Finally, it is worth noting that survivorship bias will be less important in the era of ART, as HIV mortality is lower. The assumption that women who are HIV positive at the time of interview have been infected for at least 3 years will also become more realistic as longer durations of infection become more common in the era of ART. These factors should also be considered when interpreting changes over time in the relationship between HIV and fertility from cross-sectional surveys.

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M.M. and J.W.E. conceived the concept and directed the study; M.M. performed the analysis; M.M. and J.W.E. contributed to the writing. S.G., J.N.-M., S.K., M.U., D.M. and C.N. contributed clean harmonized data and commented on drafts and B.Z. is the PI of the ALPHA network who designed the harmonization and structure of the data used for the analysis and commented on drafts.

Conflicts of interest

There are no conflicts of interest.

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