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Incident pregnancy and pregnancy outcomes among HIV-infected women in Uganda and Zimbabwe☆

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Abstract

Objective—To describe pregnancy outcomes among HIV-infected women and examine factors associated with live birth among those receiving and not receiving combination antiretroviral therapy (cART).

Methods—The present analysis included women with HIV from Uganda and Zimbabwe who participated in a prospective cohort study during 2001–2009. Incident pregnancies and pregnancy outcomes were recorded quarterly. The Kaplan–Meier method was used to estimate incident pregnancy probabilities; factors associated with live birth were evaluated by Poisson regression with generalized estimating equations.

Results—Among 306 HIV-infected women, there were 160 incident pregnancies (10.1 per 100 women-years). The pregnancy rate was higher among cART-naïve women than among those receiving cART (10.7 vs 5.5 per 100 women-years; P=0.047), and it was higher in Uganda than in Zimbabwe (14.4 vs 7.7 per 100 women-years; P<0.001). Significant associations were noted between a live birth and prenatal care (relative risk 3.9; 95% confidence interval 2.2–6.9) and illness during pregnancy (relative risk 0.8; 95% confidence interval 0.7–1.0).

Conclusion—Women not receiving cART have higher pregnancy rates than do those receiving cART, but cART use might not affect the risk of adverse pregnancy outcomes. Timely prenatal care and monitoring of illnesses during pregnancy should be incorporated into treatment services for HIV-infected women.

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Conflict of interest

The authors have no conflicts of interest.

Keywords

Antiretroviral therapy; HIV; Pregnancy outcomes; Uganda; Zimbabwe

1. Introduction

Women of reproductive age carry the largest burden of the HIV epidemic in Uganda and Zimbabwe, meaning that it is important to understand the fertility desires of these women. Uganda has one of the highest fertility rates worldwide (6.3 children per woman), whereas the fertility rate in Zimbabwe is lower at 3.4 children per woman [1]. Fertility desires among HIV-infected women are strong and are strengthened further by improved health outcomes from the initiation of combination antiretroviral therapy (cART) [2–4].

During pregnancy, cART use is highly recommended to reduce vertical HIV transmission [5]. In 2013, WHO recommended an increase of the CD4 threshold for cART initiation to 500 cells per mm^3, and the provision of lifelong cART for all pregnant and breastfeeding HIV-infected women, irrespective of their CD4 count (Option B+). In response, several Sub-Saharan African countries, including Uganda, Malawi, Kenya, and Rwanda, have adapted national guidelines to provide Option B+ [5–7]. Given the new international guidelines, the number of pregnancies among HIV-infected women is expected to increase dramatically.

Both cART and proper prenatal care are essential for pregnant HIV-infected women, for the benefit of their own health and for the safe delivery of a healthy infant. Infection with HIV is associated with adverse pregnancy outcomes such as low birth weight, abortion, and stillbirth [8–10]. Lack of adequate prenatal care partly explains this association. Women infected with HIV who receive proper prenatal care are more likely to have a successful birth outcome [11]. However, HIV-specific data (e.g. CD4 counts and cART use) and follow-up data on cART use and pregnancy outcomes among HIV-infected women are lacking. Understanding of pregnancy rates and birth outcomes among HIV-infected women has substantial implications for sexual, reproductive, and HIV health services, particularly in settings with a high prevalence of HIV.

The present paper describes pregnancy rates and birth outcomes among HIV-infected women who participated in a multicenter, 9-year prospective cohort study conducted in Uganda and Zimbabwe before Option B+ was developed [12,13]. The overall objective of the present analysis was to examine the pregnancy outcomes among HIV-infected women receiving cART and those who had never received cART. Specifically, the aims were to determine the number of incident pregnancies and the pregnancy rate by cART use; to describe the pregnancy and delivery characteristics and birth outcomes; and to examine factors associated with a live birth outcome.

2. Materials and methods

The present analysis included women from Uganda and Zimbabwe who acquired HIV infection while participating in the Hormonal Contraception and Risk of HIV Acquisition (HC-HIV) study [12] and who went on to participate in the Hormonal Contraception and

HIV-1 Genital Shedding and Disease Progression (GS) study [13] between March 12, 2001, and January 6, 2010 (last follow-up visit). The cohort study and present analysis were approved by the institutional review boards of the collaborating institutions (RTI International, Research Triangle Park, NC, USA; University Hospitals Case Medical Center, Cleveland, OH, USA; Uganda National Council for Science and Technology; and Medical Research Council of Zimbabwe). All women provided written informed consent before study participation.

Women were eligible for enrollment in the HC-HIV study if they were aged 18–35 years, were not pregnant, were not infected with HIV-1, were sexually active, and reported not having used a hormonal contraceptive method, depot medroxyprogesterone acetate (DMPA), or a combination oral contraceptive (COC) for at least 3 months, or reported not having used any other hormonal contraceptive besides COCs or DMPA [12]. Women using any other form of hormonal contraception were not eligible because the study specifically investigated the effects of using DMPA or COCs versus not using hormonal contraception, and thus women using other forms of hormonal contraception were excluded from the comparison group. Intrauterine device use was uncommon but was allowed in the comparison group. Women with a hysterectomy and those with a spontaneous or therapeutic abortion within 10 days of enrollment were ineligible for participation. As part of the HC-HIV Study, HIV testing was conducted quarterly. If study participants became HIV-infected, they were informed of the GS study and, if interested, they were enrolled as soon as possible.

Participants who provided informed consent to participate in the GS study were interviewed in the local language to collect data on sexual behavior, reproductive health, contraceptive history, and cART use [13]. During the period considered in the present analysis, the most commonly used cART regimen in each participating country was lamivudine/zidovudine plus nevirapine, which comprised more than 90% of the cART regimens used by women in the study. The contraceptives used as part of the study (DMPA and COCs) were provided free of charge. The study participants also received male and female condoms free of charge.

At the enrollment visit for the GS study, the study clinicians conducted a standardized physical (including pelvic) examination and collected specimens for the purposes of testing for reproductive tract infection (RTI) and sexually transmitted infection (STI), and pregnancy; cervical smears; lymphocyte phenotyping; and determination of the plasma and cervical viral load. The participants were tested for RTIs and pregnancy using urine human chorionic gonadotropin (hCG) testing as previously described [12,13]. The birth outcomes among pregnant participants were self-reported and collected at the first regularly scheduled study visit following the end of pregnancy.

Follow-up visits were conducted at 4, 8, and 12 weeks following enrollment and then at 12-week intervals. The follow-up procedures were similar to those at the enrollment visit and included standardized physical and pelvic examination; specimen collection for RTI, STI, and pregnancy testing; and self-reported cART use. Participants who developed severe symptoms of HIV infection (WHO clinical stage 4 or severe stage 3) and those with two

CD4 counts of 200 cells per mm^3 or less within 6 months were offered cART and trimethoprim–sulfamethoxazole, in accordance with the national guidelines for antiretroviral therapy in place during the study period.

The present analysis included HIV-infected women who had a confirmed pregnancy using urine hCG testing. Pregnancies that were estimated (e.g. on the basis of the conception date) to have started before the estimated date of HIV infection were excluded from the analysis (n=13). The date of HIV infection was estimated as the midpoint between the first positive HIV test and the last previous negative HIV test. If a woman had a negative enzyme immunoassay result and a positive polymerase chain reaction result at a study visit, the estimated HIV infection date was 15 days before the visit date. Given that enrollment into the GS Study occurred in a prospective fashion, it was possible to obtain the women's age at the HIV infection date.

The baseline characteristics, pregnancy outcomes, and delivery characteristics were analyzed by country using the χ^2 or Fisher exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. The Kaplan–Meier method was used to estimate incident pregnancy probabilities for women receiving cART and women who were cART-naïve. For the present analysis, multiple pregnancies per woman were included and cART use was determined at the time of each pregnancy.

To evaluate factors associated with live birth versus spontaneous abortion or fresh stillbirth, relative risks (RRs) and 95% confidence intervals (CIs) were calculated using generalized estimating equations with a Poisson distribution, a log link, and an exchangeable correlation matrix to account for the clustering effect of multiple pregnancies per woman. Multivariable models included factors that were associated with live birth at a level of $P \leq 0.10$ in the bivariable analysis. A priori factors included in the bivariable analysis were cART use during pregnancy, prenatal care, illness during pregnancy, pregnancy complications, baseline CD4 count, and age at labor. Illness during pregnancy was assessed on the basis of the self-reported response to the question "When you were pregnant, but before labor and delivery, did you have any illness of any kind?" Pregnancy complications were assessed on the basis of the self-reported response to the question "When you were pregnant, but before labor and delivery, did you have any complications related to pregnancy?" Women who responded "yes" to either question were then asked, "What illnesses or complications did you have?"

All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA). $P<0.05$ was considered statistically significant.

3. Results

Of the 306 women contributing to the present analysis, 127 (41.5%) were from Uganda and 179 (58.5%) were from Zimbabwe. The median age at the estimated infection date for both Uganda and Zimbabwe was 26 years (Table 1). The proportion of pregnant women living with their partners was higher in Zimbabwe than in Uganda, and women in Zimbabwe had more years of schooling than did those in Uganda. Overall, the median CD4 count at GS

study enrollment was 547.5 cells per mm^3. This figure was higher among pregnant women in Uganda than among those in Zimbabwe.

During the 9-year study period, there were 160 incident pregnancies with an overall rate of 10.1 pregnancies per 100 women-years (Table 2). The cumulative pregnancy rate was higher among cART-naïve women than among women receiving cART (10.7 vs 5.5 per 100 women-years; P=0.047), and it was higher in Uganda than in Zimbabwe (14.4 vs 7.7 per 100 women-years; P<0.001) (Table 2, Figure 1). The pregnancy rates among women using cART were noticeably lower than among those who were cART-naïve in both countries.

Women receiving cART were more likely to receive prenatal care than were cART-naïve women (75.0% vs 58.7%) (Table 3). The median time when prenatal care was started was at 6 months of pregnancy (IQR 4–7) among women receiving cART and at 5 months (IQR 4–7 months) among cART-naïve women. In both groups, half the women received prenatal care from a hospital. Reports of maternal illness during pregnancy were more common among cART-naïve women than among those receiving cART (19.1% vs 13.3%), the primarily reported illnesses being malaria, fever, and headache. Similar proportions of cART-naïve (12.9%) and cART-receiving (12.5%) women reported pregnancy complications such as preterm premature rupture of membranes; all complications occurred at or before 30 weeks of pregnancy.

Pregnancy outcomes were known for 152 pregnancies (Table 3). Women receiving cART were more likely to deliver at 37 weeks or later (61.1%), to deliver at a private hospital or clinic (61.1%), and to have a live birth (77.8%) when compared with cART-naïve women. The reported rates of spontaneous and therapeutic abortion were the same in both groups. Most women in either group delivered neonates with a birth weight of 2.5 kg or more.

In the bivariable analysis, cART use during pregnancy and prenatal care were associated with an increased relative risk of having a live birth, whereas reported illness during pregnancy was associated with a decreased relative risk of having a live birth (Table 4). Pregnancy complications, baseline CD4 count, and age at labor were not associated with having a live birth.

The final multivariable model included cART use during pregnancy, prenatal care, illness during pregnancy, and pregnancy complications. During the 9-year study period, a live birth was 3.9 (95% CI 2.2–6.9) times more likely to occur among women who had received prenatal care than among those who had not received prenatal care, and it was 0.8 (95% CI 0.7–1.0) times less likely to occur among women who reported illness during pregnancy than among those who did not.

4. Discussion

In the present multisite prospective cohort studied before the development of Option B+, most HIV-infected women with pregnancies were likely to receive prenatal care, deliver at 37 weeks or later, have a live birth, and deliver neonates with a normal birth weight (≥2.5 kg). The pregnancy incidence rate was higher among cART-naïve women than among

women taking cART. Prenatal care and lack of illness during pregnancy were significantly associated with having a live birth among HIV-infected women in Uganda and Zimbabwe.

The present study found a nearly doubled pregnancy rate among cART-naïve women (10.7 per 100 women-years) when compared with women receiving cART (5.4 per 100 women-years), contradicting previous findings that incident pregnancies were significantly more common among women receiving cART than among cART-naïve women [14,15]. Differences in terms of fertility desire, which was not investigated in the present study, could explain this difference in incident pregnancies between cART-naïve women and women receiving cART [16,17]. Fertility desires and incidence pregnancies among cART-naïve individuals were probably higher than among those receiving cART, because they were younger and had higher CD4 counts, and therefore, healthier with less progression of HIV [14,18]. Furthermore, it is important to note that up to 65% of pregnancies are self-reported as unintentional in Sub-Saharan Africa [19]. Although not specifically evaluated, the present high rate of incident pregnancies among cART-naïve women could be attributable to unplanned pregnancies, despite study participants receiving free contraceptives and counseling [20].

The associations between a live birth and prenatal care and lack of illness during pregnancy highlight the life-saving potential of prenatal care. Prenatal care services provide the opportunity to monitor and treat underlying or concurrent illnesses during pregnancy, which is particularly important for HIV-infected women. Notably, only 61% of the women in the present cohort received prenatal care, a percentage that is markedly lower than the previous estimate of 71% for pregnant women in Sub-Saharan Africa who received at least one prenatal care visit with a skilled attendant [21]. This difference could be partly attributable to the 34% of women who reported having had a spontaneous or therapeutic abortion before receiving prenatal care. This probably explains the strong association between prenatal care and live birth in the present study. Among the women who did receive prenatal care, the first visit was completed by month 5 of the pregnancy. WHO recommends completion of the first prenatal care visit by the end of the first trimester [22]. The results identify the need to improve linkages to timely prenatal care, especially among HIV-infected women, to prevent illness during pregnancy and to facilitate positive outcomes for both mother and infant.

The present finding of a high pregnancy rate contributes quantitative data to augment the findings from previous qualitative studies conducted in Sub-Saharan Africa [23,24] that demonstrated strong fertility desires among HIV-infected women. Likewise, the present data support the findings from previous studies conducted in Zimbabwe and Uganda [2,4] that also demonstrated women's desire for children despite their positive HIV status or the perceived risk of HIV transmission to their infant. The cumulative pregnancy rate of 10.1 per 100 women-years in the present study is remarkably higher than the rate of 7.8 per 100 women-years found among HIV-infected women in another multicountry study conducted in Sub-Saharan Africa [14], and is perhaps attributable to the inclusion of Ugandan women (Uganda is a country with a very high fertility rate).

The present analysis has several limitations. First, it could have been susceptible to selection bias because the included women were part of a large multisite clinical trial examining the

use of hormonal contraception and the risk of HIV acquisition, and were therefore not representative of all HIV-infected women within the region. However, a high proportion of the women invited to participate in the trial did agree to enroll. Furthermore, the women included in the present analysis were provided free hormonal contraceptives as part of a large multisite clinical trial, limiting the generalizability of the results to HIV-infected women with limited access to hormonal contraceptives and family planning counseling. Future studies using clinical data from prenatal care and antiretroviral therapy clinics might more appropriately represent this population. The present analysis relied on self-report, and recall was likely to be high because the women were questioned about their pregnancy outcomes soon after the completion of their pregnancy. However, it is possible that women with an adverse pregnancy outcome were more likely to report not using cART. This could partly explain the small proportion of HIV-infected women reporting cART initiation at the time of pregnancy. The paucity of HIV-infected women who initiated cART could explain the lack of a significant association between cART use and live birth in the multivariable analysis. A larger sample size might have increased the precision of the estimates, particularly for the association between prenatal care and live birth. Lastly, infants were not followed up during the study and it was therefore not possible to determine their HIV status and other adverse infant health outcomes related to pregnancy.

The strengths of the present analysis include the fact that the women were followed up for nearly a decade after HIV infection. The prospective nature of the present study allowed for the detection and follow-up of incident pregnancies among women who were HIV-infected. It was also possible to compare incident pregnancy rates and factors associated with live birth across two countries with high HIV prevalences, where the implemented protocols for the overall study were identical.

As expanded cART becomes more common in Sub-Saharan Africa, HIV care and treatment services must target HIV-infected women to address their fertility issues. Given the high rate of incidence pregnancy among HIV-infected women, integration of fertility and contraception counseling throughout the entire HIV spectrum of care (testing, care, and treatment) is essential to ensure positive pregnancy outcomes and prevent mother-to-child transmission. Further studies that delineate the motivations for pregnancy among cART-naïve women will help to inform fertility and contraception counseling sessions. The present results emphasize that timely and appropriate prenatal care is urgently needed among women with HIV infection, as is monitoring of pregnancy complications and illnesses. Women living with HIV need integrated services that address fertility-related issues to optimize the health outcomes for mother and child.

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Synopsis

In Uganda and Zimbabwe, combination antiretroviral therapy for HIV is associated with lower pregnancy rates but does not affect the risk of adverse pregnancy outcomes.

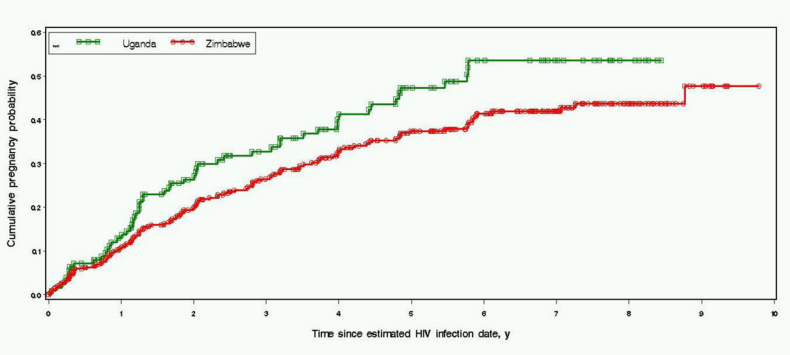

Figure 1.

Kaplan–Meier estimation of the pregnancy probability by time since estimated infection date. Log-rank test for the difference between the groups: *P*=0.0027.

Table 1

Characteristics of included women.[a]

Characteristic	Uganda (n=127)	Zimbabwe (n=179)	Total (n=306)	*P* value
Age at estimated infection date, y	26 (23–30)	26 (23–30)	26 (23–30)	0.786
Living with partner [b]	74 (58.3)	126 (70.4)	200 (65.4)	0.028
Number of years in school [c]	8 (6–10)	11 (9–11)	10 (7–11)	<0.001
Age at first pregnancy, y	27 (25–29)	26 (25–30)	27 (25–29)	0.922
CD4, cells per mm^3 [b]	613 (478–783)	495 (369–645)	548 (413–684)	<0.001

[a] Values are given as median (interquartile range) or number (percentage), unless indicated otherwise.

[b] At the enrollment visit for the Hormonal Contraception and HIV-1 Genital Shedding and Disease Progression study.

[c] At the screening visit for the Hormonal Contraception and Risk of HIV Acquisition study.

Table 2

Pregnancy rate by cART use at start of pregnancy.[a,b]

Study site	No cART use	cART use	Total	*P* value
Uganda	78/513 (15.2)	4/56 (7.1)	82/569 (14.4)	0.142
Zimbabwe	72/887 (8.1)	6/127 (4.7)	78/1014 (7.7)	0.233
Total	150/1400 (10.7)	10/183 (5.5)	160/1583 (10.1)	0.047

Abbreviation: cART, combination antiretroviral therapy.

[a] Values are given as number/woman-years (incidence rate per 100 woman-years) unless indicated otherwise.

[b] Multiple pregnancies per woman are included. Thirteen pregnancies were excluded from the analysis because the pregnancy start date was before the estimated HIV infection date.

Table 3

Characteristics of pregnancies by cART use.[a,b]

Characteristic	No cART use (n=142)	cART use (n=18)	Total (n=160)	*P* value
Prenatal care				
Care received	74 (52.1)	12 (66.7)	86 (653.8)	0.210
Pregnancy month when started to receive care	5 (4–7)	6 (5–7)	5 (4–7)	0.307
Location				
Hospital	37 (26.0)	6 (33.3)	43 (26.9)	
Health center	31 (21.8)	6 (33.3)	37 (23.1)	
Private hospital/clinic	6 (4.2)	0	6 (3.8	0.572
Events during pregnancy				
Illness	24 (16.9)	2 (11.1)	26 (16.3)	0.738
Pregnancy complications	16 (11.3)	2 (11.1)	18 (11.3)	>0.99
Delivery				
Pregnancy duration, wk				
<20	52 (36.6)	4 (22.2)	56 (35.0)	
20 to <28	7 (4.9)	0	7 (4.4)	
28 to <32	5 (3.5)	0	5 (3.31)	
32 to <37	6 (4.2)	2 (11.1)	8 (5.0)	
≥37	66 (46.5)	11 (61.1)	77 (48.1)	0.170
Missing [c]	6 (4.2)	1 (5.6)	7 (4.4)	
Location				
Home	2 (1.4)	0	2 (1.3)	
Hospital	41 (28.9)	7 (38.9)	48 (30.0)	
Health center	27 (19.0)	7 (38.9)	34 (21.3)	
Private hospital/clinic	6 (4.2)	0	6 (3.8)	0.705
Missing [c]	66 (46.5)	4 (22.2)	70 (43.8)	
Delivery method				
Cesarean	10 (7.0)	0	10 (6.3)	0.351
Pregnancy outcome				
Live birth	80 (56.3)	14 (77.8)	94 (58.8)	
Fresh stillbirth	4 (2.8)	0	4 (2.5)	
Spontaneous abortion	26 (18.3)	1 (5.6)	27 (16.9)	
Therapeutic abortion	26 (18.3)	1 (5.6)	27 (16.9)	0.259
Missing [c]	6 (4.3)	2 (1.1)	8 (0.4)	
Birth weight, kg				
≥2.5	65 (45.8)	12 (66.7)	77 (48.1)	
<2.5	10 (7.0)	2 (11.1)	12 (7.5)	
Unknown	67 (47.2)	4 (22.2)	71 (44.4)	>0.99

Abbreviation: cART, combination antiretroviral therapy.

[a] Values are given as number (percentage) or median (interquartile range), unless indicated otherwise.

[b] Multiple pregnancies per woman allowed.

[c] Not included in calculation of the *P* value.

Table 4

Characteristics associated with having a live birth.

Characteristic	Bivariable analysis		Multivariable analysis	
	RR (95% CI)	*P* value	RR (95% CI)	*P* value
cART use during pregnancy	1.3 (1.1–1.5)	0.006	1.2 (1.0–1.4)	0.134
Prenatal care	4.4 (2.7–8.0)	<0.001	3.9 (2.2–6.9)	<0.001
Illness during pregnancy	0.6 (0.4, 1.0)	0.036	0.8 (0.7–1.0)	0.037
Pregnancy complications	0.6 (0.3, 1.0)	0.056	0.7 (0.4–1.2)	0.192
Baseline CD4, cells per mm^3				
<350	1.1 (0.8–1.5)	0.678	–	–
350–500	1.0 (0.8–1.3)	0.909	–	–
>500	Ref.	–	–	–
Age at labor, y				
21–25	1.3 (1.0–1.6)	0.105	–	–
26–28	1.2 (0.9–1.6)	0.154	–	–
≥29	Ref.	–	–	–

Abbreviations: RR, relative risk; CI, confidence interval; cART, combination antiretroviral therapy.