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A prospective study of the effect of pregnancy on CD4 counts and plasma HIV-1 RNA concentrations of antiretroviral-naive HIV-1 infected women

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Abstract

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Conflicts of Interest
No conflicts of interest were reported.

Background—In HIV-1 infected women, CD4 count declines occur during pregnancy, which has been attributed to hemodilution. However, for women who have not initiated antiretroviral therapy (ART), it is unclear if CD4 declines are sustained beyond pregnancy and accompanied by increased viral levels, which could indicate an effect of pregnancy on accelerating HIV-1 disease progression.

Methods—In a prospective study among 2269 HIV-1 infected ART-naïve women from 7 African countries, we examined the effect of pregnancy on HIV-1 disease progression. We used linear mixed models to compare CD4 counts and plasma HIV-1 RNA concentrations between pregnant, postpartum and non-pregnant periods.

Results—Women contributed 3270 person-years of follow-up, during which time 476 women became pregnant. In adjusted analysis, CD4 counts were an average of 56 (95% CI 39-73) cells/mm^3 lower during pregnant compared to non-pregnant periods and 70 (95% CI 53-88) cells/mm^3 lower during pregnant compared to postpartum periods; these results were consistent when restricted to the subgroup of women who became pregnant. Plasma HIV-1 RNA concentrations were not different between pregnant and non-pregnant periods (p=0.9) or pregnant and postpartum periods (p=0.3). Neither CD4 counts nor plasma HIV-1 RNA levels were significantly different in postpartum compared to non-pregnant periods.

Conclusion—CD4 count declines among HIV-1 infected women during pregnancy are temporary and not sustained in postpartum periods. Pregnancy does not have a short term impact on plasma HIV-1 RNA concentrations.

Keywords

pregnancy; HIV-1; CD4 count; plasma HIV-1 RNA concentration

Background

In women with HIV-1 infection, immune function declines through the natural course of HIV-1 disease. Pregnancy is common among HIV-1 infected women and the interaction between HIV-1 and pregnancy has been a topic of biologic and behavioral investigation.[1, 2] During pregnancy, changes to the maternal immune system, including decreased levels of circulating CD4 lymphocytes, are normal.[3] It is important to understand how these natural changes may be impacted by HIV-1 infection and whether any deleterious effects are sustained postpartum.

Studies examining the long term impacts of pregnancy on HIV-1 disease progression prior to the initiation of antiretroviral therapy (ART) have employed different methods and come to inconsistent conclusions.[4-7] A meta-analysis of eight studies concluded that there may be a moderate increase in the risk of an AIDS-defining illness during pregnancy, especially in developing countries.[5] A more recent study used a prediction model to estimate that although HIV-1 infected ART-naïve women who became pregnant generally had higher CD4 counts than women who did not become pregnant (i.e. a “healthy woman” effect) , the rate of CD4 count decline was greater after pregnancy and this more rapid rate was predicted to be sustained in the years following pregnancy.[8] Studies of women using ART, however, have not seen any indication of accelerated progression to death or AIDS stemming from pregnancy.[9] For women who have not initiated ART prior to or during pregnancy, it remains unknown whether pregnancy results in sustained declines in immune function (measured through CD4 count) and increases in virologic replication (measured by plasma HIV-1 RNA concentrations) that would have effects after pregnancy.

Given high fertility rates among some populations of HIV-1 infected women, particularly in high prevalence settings such as sub-Saharan Africa, understanding the effects of pregnancy

on HIV-1 disease progression is a public health priority.[1, 10] In a large cohort of women from southern and East Africa with chronic HIV-1 infection, we evaluated the effect of pregnancy on CD4 counts and plasma HIV-1 RNA concentrations and whether any changes in these markers were sustained in the first year following pregnancy.

Methods

Study participants

Between 2004 and 2008, we conducted a randomized clinical trial of acyclovir to prevent HIV-1 transmission from 3408 individuals dually-infected with HIV-1 and herpes simplex virus type 2 (HSV-2) to their HIV-1 uninfected sexual partners (the Partners in Prevention HSV/HIV Transmission Study).[11] Participants were enrolled at 14 sites in 7 countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia) in southern and eastern Africa. At enrollment, HIV-1 infected participants were at least 18 years of age, sexually active with their study partner, not pregnant, not using ART, without AIDS-defining conditions, and had a CD4 count ≥250 cells/mm^3. HIV-1 infected members of these HIV-1 serodiscordant partnerships were randomized 1:1 to receive acyclovir (400 mg orally twice daily) or matching placebo and followed monthly for up to 24 months. In the final study analysis, acyclovir did not reduce the risk of HIV-1 transmission but it did result in a 0.25 $\log_{10}$ copies/ml (95% CI, 0.22-0.29; $p<0.001$) decrease in plasma HIV-1 RNA concentrations and a modest decline in the rate of HIV-1 disease progression for the HIV-1 infected partners.[12, 13]

For the present analysis, HIV-1 infected women (2269 of the 3408 HIV-1 infected participants in the trial) were included. Participants attended monthly clinic visits for study drug provision and HIV-1 care services, including individual and couples risk reduction counseling, free condoms, and treatment of sexually transmitted infections (STIs). Women who became eligible for ART use according to national guidelines at the time were referred to nearby clinics to receive treatment. Data on ART use and clinical symptoms were collected using interviewer-administered questionnaires. Women who became pregnant during follow up had study drug (acyclovir or placebo) withheld during pregnancy.

Laboratory testing

CD4 counts were measured every 6 months using FacsCount or FacsCalibur instrumentation (BD Biosciences, San Jose, USA) and plasma HIV-1 RNA concentrations were measured quarterly during the first year of follow up and every 6 months thereafter using the COBAS TaqMan real-time HIV-1 RNA assay, version 1.0 (Roche Diagnostics, Indianapolis, IN) with 240 copies/mL being the lower limit of quantification. Of all CD4 count measurements conducted, 7412 (77.1%) were from women who did not become pregnant during the study, 225 (2.4%) were from the first trimester of pregnancy, 200 (2.1%) from the second trimester, 108 (1.1%) from the third trimester and 546 (6.8%) were from postpartum period.

Measurement of pregnancy

Urine pregnancy tests were performed at enrollment and during quarterly study visits. Date of last menstrual period (LMP), estimated date of delivery, and pregnancy outcome were collected with standardized questionnaires. We defined the start of pregnancy as the date of LMP and the end of pregnancy as the date of delivery or pregnancy loss. Complete data on LMP and date of delivery were available for 96% of pregnancies observed during the study; for the remaining pregnancies, we estimated start and end dates using the reported duration of the pregnancy (based on maternal history) and either the LMP or date of delivery.

Statistical analysis

We used linear mixed effects models with a random intercept and a compound symmetry correlation structure to estimate the average difference in CD4 count and plasma HIV-1 RNA levels during several time periods: pregnancy, postpartum (the time following pregnancy), non-pregnant periods (all follow up time for women who did not become pregnant and the time prior to the first pregnancy for women who became pregnant), and the time prior to the first pregnancy for women who became pregnant (the "prenatal" period). We performed analyses first for all women in the study and compared CD4 and plasma HIV-1 RNA levels among pregnant versus non-pregnant and postpartum periods as well as postpartum and non-pregnant periods. We then repeated the analyses restricted only to women who experienced pregnancy during the study (thus comparing prenatal, pregnant and postpartum periods among these women. All models accounted for time on study. For women who had multiple pregnancies, the time between pregnancies was considered postpartum time since second pregnancies occurred a median of 5.8 months after the first pregnancy ended.

Follow up time was censored in all analyses when women initiated multi-drug ART (3.1% of study time); we did not censor for single or dual drug ART use that was associated only with pregnancy (e.g. single dose nevirapine use) because it is unlikely that limited duration ART would have substantial impact on subsequent CD4 counts or plasma HIV-1 RNA levels. We determined *a priori* that full multivariate models would be adjusted for the enrollment CD4 count or plasma HIV-1 RNA concentration. Additional adjustment accounted for treatment arm (acyclovir or placebo) and study drug dispensing (any or none), to account for the effect of acyclovir on reductions in plasma HIV-1 RNA concentration, increases in CD4 count, and that study drug was discontinued during pregnancy. Using the same statistical modeling methods, we conducted separate sensitivity analyses to account for early pregnancy losses (by excluding pregnancies that terminated at <20 weeks) and multiple pregnancies in a single woman (by including only these pregnancies) that may have a different impact on disease progression. SAS 9.3 (Cary, NC, USA) was used for all analyses.

Results

Participant characteristics

For the 2269 women enrolled, the median age was 30 (interquartile range [IQR] 25.3-34.8, Table 1). Most women were married with a median of 2 children and 8 years of education. In the month prior to enrollment, women reported a median of 4 (IQR 2-8) sex acts with their study partner and 28.7% of women reported having unprotected sex. The median CD4 count was 483 (IQR 355-663) cells/mm^3, 472 (IQR 348-655) cells/mm^3 among women who did not go on to have a pregnancy and 507 (IQR 378-689) cells/mm^3 among women who later became pregnant. The median plasma HIV-1 RNA concentration was 3.9 (IQR 3.2-4.5) log_{10} copies/mL.

Pregnancy during follow up

During follow up for this analysis, 476 (21.0%) women became pregnant (29 women had more than 1 pregnancy) and the pregnancy incidence rate was 15.4 per 100 person years (505 pregnancies/3270 years). 7.2% of total follow up time was during pregnant periods and 6.8% was during postpartum periods. Women who became pregnant contributed a median of 7.2 (IQR 4.0-13.0) months of time during the prenatal period, 7.1 (IQR 3.1-9.0) months pregnant and 7.9 (IQR 4.0-11.9) months "postpartum," between the end of pregnancy and study exit. 219 (43.4%) pregnancies ended in a live birth, 144 (28.5%) pregnancies ended in a pregnancy loss, 3 (0.60%) were ectopic pregnancies, 133 (26.3%) were ongoing at the

time of study completion, and the outcome was unknown for 6 (1.2%) pregnancies. Of pregnancies that ended in a pregnancy loss, 114 (79.2%) ended before reaching 20 weeks gestation. ART was used during 177/219 (80.8%) pregnancies that resulted in a live birth, including single and dual drug regimens during delivery for 102/219 (46.6%) pregnancies and multi-drug ART during the pregnancy for 75/219 (34.3%) pregnancies.

Effect of pregnancy on CD4 counts and plasma HIV-1 RNA concentrations

In the fully adjusted model, CD4 counts were lower during pregnant than non-pregnant periods (average difference in CD4 count: 56 cells/mm^3, 95% CI 39-73) and postpartum periods (average difference in CD4 count: 70 cells/mm^3, 95% CI 53-88, Table 2). The average CD4 count was similar, however, during postpartum periods and non-pregnant periods (p=0.1). HIV-1 RNA concentration did not statistically differ between pregnant and non-pregnant periods (p=0.9) nor pregnant and postpartum periods (p=0.3). Prior to full adjustment, we observed a moderately higher level of plasma HIV-1 RNA concentration during pregnancy relative to the postpartum period (average difference in plasma HIV-1 RNA concentration = 0.07, 95% CI 0.01-0.03). This difference was no longer present, however, after adjusting for randomization arm and pill dispensing suggesting that the unadjusted association was a result of the effect of acyclovir to reduce plasma HIV-1 levels. [12]

When limited to the subgroup of women who became pregnant, CD4 counts were lower during pregnancy than during prenatal periods (adjusted average difference in CD4 count = 51 cells/mm^3, 95% CI 30-72) or postpartum periods (adjusted average difference in CD4 count = 70 cells/mm^3, 95% CI 51-90). Consistent with the results for the cohort as a whole, there was no difference in CD4 counts between prenatal and postpartum periods (p=0.1). Plasma HIV-1 RNA concentration levels were similar across comparisons of pregnant and prenatal (p=0.7), pregnant and postpartum (p=0.7) and prenatal and postpartum (p=0.9) periods.

To account for early pregnancy losses that may have a different impact on disease progression than full term pregnancies, we conducted a sensitivity analysis that excluded pregnancies that were <20 weeks duration by censoring follow up time at the beginning of a pregnancy that ended in an early loss (9.3% of pregnant and 5.7% of postpartum follow up). The results from this were not different from the primary results. In a separate sensitivity analysis, we limited the dataset to 29 women who experienced multiple pregnancies during the study and saw similar changes to CD4 count but no sustained change in postpartum periods and no change in HIV-1 RNA concentration (data not shown).

Discussion

In this prospective study of African women with chronic HIV-1 infection, we found that CD4 counts were lower during pregnancy than during prenatal and non-pregnant periods but these lower CD4 counts were not sustained in the postpartum period. Thus, a drop in CD4 count that is commonly experienced by HIV-1 infected women during pregnancy does not appear to result in sustained immunologic effects during the first year following pregnancy. Our results are consistent with the process of hemodilution during pregnancy and a return to previous immune function levels following the end of pregnancy.[3] These findings suggest that pregnancy does not result in subsequent accelerated HIV-1 disease progression by affecting immune function or by increasing HIV-1 levels, as minor changes were not sustained postpartum.

Our study is limited by the length of time women were followed postpartum. Further investigation is required to understand whether the immunologic rebound that we observed

is maintained in the years following the pregnancy, as was demonstrated in a recent prediction model.[4] An additional consideration is whether breastfeeding periods have a different level of influence on immune function or viral levels; we did not record the duration of breastfeeding in this study. This question is difficult to study because women who become pregnant are different than women who do not become pregnant and thus traditional survival analysis with time-limited follow up data may suffer from selection bias. We conducted sensitivity analyses to restrict our data to “healthy pregnancies” and then to look at women with multiple pregnancies, with similar results. We chose to use a linear mixed model to examine the difference in disease progression markers, in lieu of defining a threshold endpoint, which can suffer from survival bias if exposure groups are defined based on a future experience (i.e. pregnancy).[14]

Pregnancy is common among women living with HIV-1, especially after ART initiation which often brings restored health and fertility desire.[15-17] While there appears to be little risk of pregnancy accelerating a woman's HIV-1 disease progression, becoming pregnant indicates a lack of condom use prior to pregnancy and potential risk of HIV-1 transmission to an uninfected male partner. Additionally, pregnant periods are often accompanied by less frequent condom use.[1, 18] Unintended pregnancy is often associated with increased morbidity and mortality and a priority for programs to prevent mother to child HIV-1 transmission.[19] Integrated reproductive health programs that proactively engage couples to consider their fertility intentions and use effective contraception until fertility is desired, plan future pregnancies, and incorporate HIV-1 prevention are of public health importance.[20] Planning allows couples to employ low technology harm reduction strategies in order to reduce the risk of HIV-1 transmission to the uninfected male partner– strategies include unprotected sex timed to peak fertility days, self-insemination, ART, PrEP use, male circumcision and treatment of sexually transmitted infections – and use ART to prevent vertical transmission.[21, 22] Couples have indicated a desire for knowledge and discussions about these options with healthcare workers and willingness to use them.[23]

In 2012, the World Health Organization recommended that national PMTCT programs consider multi-drug ART initiation during pregnancy followed by lifelong use for HIV-1 infected women to achieve HIV-1 viral suppression, prevent maternal to child HIV-1 transmission, and maintain their health during pregnancy and thereafter (i.e. Options B or B +).[24] PMTCT guidelines, including the duration and complexity of ART prophylaxis regimens, have evolved rapidly since the first WHO guidelines were published in 2000.[25] Twenty percent of pregnancies in our study did not have ART prophylaxis during the pregnancy or at delivery, which likely reflects programmatic challenges and the gradual implementation of ART in PMTCT programs during 2004-2008 when our data were collected.[25] ART use during and after pregnancy is a critical public health strategy to reduce vertical HIV-1 transmission as well as to provide clinical benefits to the mother, but resources, health system factors, and personal factors provide challenges for universal implementation and retention in ART programs.[26, 27]. In addition, many women decline ART initiation when it is first recommended or experience system delays when trying to start.

Our data support the conclusion that even prior to ART initiation, CD4 declines during pregnancy are modest and short term for women with HIV-1 infection. As PMTCT guidelines evolve to increase coverage of ART in pregnant women, more emphasis and strategies are needed to improve ART initiation and continuation rates among women who become pregnant to ensure their maximum health status and favorable birth outcomes.

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Table 1

Characteristics of HIV-1 infected women at enrollment, median (IQR) or N (%)

	All women	Women who did not have a pregnancy	Women who became pregnant
Number of women	2269	1793	476
Demographics			
Age	30.0 (25.3-34.8)	30.9 (26.2-36.0)	26.5 (23.5-30.4)
Number of children	2 (1-3)	2 (1-3)	2 (1-3)
Education (years)	8 (6-10)	8 (6-11)	8 (6-10)
Married	1727 (76.1)	1333 (74.3)	394 (82.8)
Duration of partnership (years)	4.8 (2.1-9.2)	5.1 (2.2-9.8)	4.1 (1.9-7.1)
Sexual behavior			
Coital frequency (last month)	4 (2-8)	4 (2-8)	4 (2-7)
Any unprotected sex (last month)	650 (28.7)	502 (28.0)	148 (31.1)
Any effective contraception *	539 (23.8)	467 (26.1)	72 (15.1)
HIV clinical characteristics			
CD4 count (cells/mm^3)	483 (355-663)	472 (348-655)	507 (378-689)
Plasma HIV-1 RNA (log_{10}) copies/ml	3.94 (3.23-4.53)	3.95 (3.20-4.55)	3.92 (3.28-4.48)

* Effective contraception includes the use of hormonal methods or a copper IUD.

Table 2

Differences in CD4 count and plasma HIV-1 RNA concentration levels during A) non-pregnant, pregnant and postpartum periods and B) prenatal, pregnant and postpartum periods

	Adjusted for time in study			Adjusted for time in study and additional factors**		
	Regression coefficient	**95% CI**	**p-value**	**Regression coefficient**	**95% CI**	**p-value**
A) All HIV-1 infected women						
Average difference in CD4 count						
Pregnant vs. non-pregnant*	−65	−79, −51	<0.0001	−56	−73, −39	<0.0001
Pregnant vs. postpartum	−77	−93, −61	<0.0001	−70	−88, −53	<0.0001
Postpartum vs. non-pregnant*	+12	−3, +27	0.12	+14	−2, +30	0.1
Average difference in plasma HIV-1 RNA concentrations						
Pregnant vs. non-pregnant*	+0.04	−0.01, +0.09	0.12	+0.01	−0.05, +0.06	0.9
Pregnant vs. postpartum	+0.07	+0.01, +0.13	0.03	+0.03	−0.03, +0.10	0.3
Postpartum vs. non-pregnant*	−0.03	−0.09, +0.03	0.3	−0.03	−0.1, +0.03	0.3
B) HIV-1 infected women who experienced a pregnancy during the study						
Average difference in CD4 count						
Pregnant vs. prenatal	−57	−77, −36	<0.0001	−51	−72, −30	<0.0001
Pregnant vs. post-partum	−87	−106, −67	<0.0001	−70	−90, −51	<0.0001
Postpartum vs. prenatal	+30	+1, +59	0.04	+19	−6, +45	0.1
Average difference in plasma HIV-1 RNA concentrations						
Pregnant vs. prenatal	+0.05	−0.02, +0.13	0.2	+0.01	−0.06, +0.09	0.7
Pregnant vs. post-partum	+0.05	−0.03, +0.13	0.3	+0.02	−0.06, +0.1	0.7
Postpartum vs. prenatal	+0.01	−0.11, +0.12	0.9	−0.01	−0.11, +0.10	0.9

Follow-up time was censored when ART was initiated.

*Non-pregnant periods include time from women who did not become pregnant and prenatal periods from women who became pregnant.

**Factors in full models of CD4 count are baseline CD4 count, randomization arm, study drug bottle dispensing and time in study. Factors in full models of HIV-1 RNA concentration are baseline HIV-1 RNA concentration, randomization arm, study drug bottle dispensing, and time in study.