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Pregnancy and HIV Disease Progression in an Early Infection Cohort from Five African Countries

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Background: Understanding associations between pregnancy and HIV disease progression is critical to provide appropriate counseling and care to HIV-positive women.

Methods: From 2006 to 2011, women less than age 40 with incident HIV infection were enrolled in an early HIV infection cohort in Kenya, Rwanda, South Africa, Uganda, and Zambia. Time-dependent Cox models evaluated associations between pregnancy and HIV disease progression. Clinical progression was defined as a single CD4 measurement <200 cells/μl, percent CD4 <14%, or category C event, with censoring at antiretroviral (ART) initiation for reasons other than prevention of mother-to-child transmission (PMTCT). Immunologic progression was defined as two consecutive CD4s ≤350 cells/μl or a single CD4 ≤350 cells/μl followed by non-PMTCT ART initiation. Generalized estimating equations assessed changes in CD4 before and after pregnancy.

Results: Among 222 women, 63 experienced clinical progression during 783.5 person-years at risk (8.0/100). Among 205 women, 87 experienced immunologic progression during 680.1 person-years at risk (12.8/100). The association between pregnancy and clinical progression was adjusted hazard ratio [aHR] = 0.7, 95% confidence interval (CI): 0.2, 1.8. The association between pregnancy and immunologic progression was aHR = 1.7; 95% CI: 0.9, 3.3. Models controlled for age; human leukocyte antigen alleles A*03:01, B*45, B*57; CD4 set point; and HIV-1 subtype. CD4 measurements before versus after pregnancies were not different.

Conclusions: In this cohort, pregnancy was not associated with increased clinical or immunologic HIV progression. Similarly, we did not observe meaningful deleterious associations of pregnancy with CD4s. Our findings suggest that HIV-positive women may become pregnant without harmful health effects occurring during the pregnancy. Evaluation of longer-term impact of pregnancy on progression is warranted.

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The effect of pregnancy on HIV disease progression has been a topic of debate and uncertainty for over two decades.\textsuperscript{1} This is an issue of increasing importance since, with advances in HIV treatment, care, and prevention of mother-to-child transmission, pregnancy incidence\textsuperscript{2,6} and desire for children\textsuperscript{6–9} among HIV-infected African women are increasing while rates of unintended pregnancy remain high.\textsuperscript{10–13}

Interpretation of the current literature is complicated by use of various disease progression outcomes (e.g., decreased CD4 count, increased viral load, antiretroviral treatment [ART] initiation, and/or death), different study inclusion criteria, and low study power. A recent meta-analysis\textsuperscript{14} synthesized results from 15 observational studies with findings presented separately for various disease progression outcomes. Pregnancy was not associated with AIDS-defining illnesses among HIV+ women in 10 studies\textsuperscript{15–24} (summary pooled relative risk, RR = 0.97; 95% CI: 0.74, 1.25), although this estimate is slightly downward weighted by one study from the United States in which 71% of women were on ART (adjusted hazard ratio, aHR = 0.55; 95% CI: 0.27, 1.11).\textsuperscript{25} The only study included from an African cohort found no association between pregnancy and AIDS-defining illness in Ugandan women not using ART (aHR = 1.16; 95% CI: 0.51, 2.65).\textsuperscript{19} The review also found pregnancy was marginally associated with decreasing CD4 cell counts among HIV+ non-ART using women in four studies\textsuperscript{15,18–20} (RR = 1.41; 95% CI: 0.99, 2.02); the single study from an African cohort similarly did not find an association between pregnancy and time to CD4 <200 cells/μl in Ugandan women (aHR = 1.67; 95% CI: 0.77, 3.63).\textsuperscript{19}

Three additional studies (each assessing associations between hormonal contraceptive methods and HIV disease progression as primary outcomes) also included measures of time-varying pregnancy. One study of ART-naïve 2269 chronically HIV-infected women from five East and Southern African countries found pregnancy was associated with shorter time to CD4 count <200 cells/μl, ART initiation, or nontraumatic death (aHR = 1.45; 95% CI: 1.03, 2.04).\textsuperscript{25} Conversely, an observational study among 625 Ugandan women found no association between pregnancy and time to AIDS or death (aHR = 0.96; 95% CI: 0.62, 1.48).\textsuperscript{26} and a study among 303 women from Uganda and Zimbabwe recruited immediately after seroconversion found no association between pregnancy and time to clinical AIDS, death, or ART initiation (aHR = 1.06; 95% CI: 0.46, 2.45).\textsuperscript{27}

Understanding pregnancy-related risks HIV-infected women may face is critical to providing appropriate counseling and management of fertility intentions, decisions, and unintended pregnancy. We sought to add high-quality evidence to a varied and uncertain literature by evaluating the association between pregnancy and clinical AIDS or immunologic disease progression among women in an early infection cohort from five East and Southern African countries. We also consider changes in CD4 count before, during, and after pregnancy, hypothesizing that any immunologic changes observed during pregnancy are transient with CD4 counts rebounding after pregnancy.

**METHODS**

**Ethics**

This study was approved by the Kenya Medical Research Institute Ethical Review Committee, Kenyatta National Hospital Ethical Review Committee of the University of Nairobi, Rwanda National Ethics Committee, the Uganda Virus Research Institute Science and Ethics Committee, Uganda National Council of Science and Technology, University of Cape Town Health Science Research and Ethics Committee, University of Zambia Research Ethics Committee, Bio-Medical Research Ethics Committee at the University of KwaZulu Natal, and Emory University Institutional Review Board. All study participants provided written informed consent.

**Study Participants and Procedures**

Participant eligibility, recruitment, enrollment, follow-up, and laboratory procedures have been described.\textsuperscript{28,29} In brief, from 2006 to 2011, men and women recruited primarily from HIV incidence cohorts were enrolled from nine research centers in five countries (Kenya, Rwanda, South Africa, Uganda, and Zambia) into a multicenter cohort (“IAVI Protocol C”). Eligible participants were 18–60 years old (16– to 17-year-olds were eligible in Cape Town), had a documented HIV-negative test within the prior year, and had a subsequent positive p24-antigen enzyme-linked immunosorbent assay (ELISA) or HIV antibody test. Study visits were conducted monthly until 3 months after participants’ estimated date of HIV infection, then quarterly for 2 years, and biannually thereafter. Estimated date of HIV infection was estimated as the midpoint between first positive and last negative antibody test, 14 days before a positive p24-antigen test with a negative antibody test, or 10 days before a positive polymerase chain reaction (PCR) test with negative p24-antigen and antibody tests.

**Exposure of Interest**

For women with a positive urine pregnancy test, we created a time-dependent covariate for pregnancy status with self-reported start date (last normal menses) and end date. When the start date was missing or inconsistent with the end date, we assumed it occurred 40 weeks before the delivery date for a live birth and 12 weeks before the end date for a spontaneous or therapeutic abortion. If the end date was missing, we assumed the pregnancy had ended 40 weeks after the last normal menses for a live birth and 12 weeks after the last normal menses for a spontaneous or therapeutic abortion. If both dates were missing, the pregnancy test was assumed to be false positive. Women had at most three study visits (at 2, 5, and 8 months of pregnancy) while pregnant and could contribute data from more than one pregnancy.
Outcomes of Interest

We considered time to two primary outcomes: clinical progression to AIDS (“clinical progression”) and immunologic progression. Follow-up time started from the estimated date of HIV infection. Clinical progression was defined as a single CD4 count $<200$ cells/μl, percent CD4 $<14\%$, and/or a category C event. We censored at ART initiation (other than for prevention of mother-to-child transmission) and excluded women with set point CD4 (the number of CD4 cells immediately after primary HIV infection) $<200$ cells/μl. Category C events were defined per CDC and WHO guidelines.\(^\text{30}\) In sensitivity analyses, we extended this definition to include ART initiation (other than for prevention of mother-to-child transmission).

Immunologic progression was defined as two consecutive CD4 counts $\leq 350$ cells/μl or a single CD4 count $\leq 350$ cells/μl followed by ART initiation (other than for prevention of mother-to-child transmission) before the next CD4 measurement. We excluded women with set point CD4 $\leq 350$ cells/μl.

ART initiation was self-reported with the exception of Kenya, where treatment was prescribed and provided in-clinic. Participants were asked about reasons for initiating ART; for those reporting ART use for prevention of mother-to-child transmission, investigators confirmed the end date of therapy to prevent vertical transmission. During the course of the study, many programmatic changes were made in ART drug provision, including replacing short-course ART drug regimens to prevent mother-to-child transmission with long-term therapy. Therefore, if no end date was provided, this typically implied that drug therapy to prevent mother-to-child transmission had been superseded by long-term provision of ART.

Statistical Analysis

We restricted analyses to women less than age 40 at estimated date of HIV infection and follow-up was through September 2014. Baseline characteristics were described and were stratified by the outcomes of interest. Unadjusted pregnancy rates were calculated as the number of pregnancies per 100 person-years at risk (person-years at risk), excluding person-time during pregnancy. Rates, rate ratios, 95\% confidence intervals (CIs), and $P$ values were calculated overall and by disease progression outcomes assuming Poisson distributions. Unadjusted disease progression rates were similarly calculated, stratified by time-varying pregnancy, and covariates of interest.

Time-dependent Cox models with robust standard errors and the Efron method for handling ties quantified the effect of pregnancy on progression. Baseline covariates known to be associated with progression were included in all adjusted models: age at estimated date of HIV infection ($<30$ years, $\geq 30$ years); presence of human leukocyte antigen (HLA) alleles A*03:01, B*45, and B*57; CD4 set point; and HIV-1 infecting subtype. CD4 set point was defined as the first CD4 cell count measured after day 69 from estimated date of infection. Day 70 begins the window for the month three visit by which time CD4 cell count is expected to be past its acute phase nadir.\(^\text{11}\) Given national differences in ART initiation guidelines, we examined the effect of country on progression. However, due to strong associations between country and HIV-1 infecting subtype (determined by DNA polymerase or “pol” genotype sequencing), country was not included in final adjusted models.

Generalized estimating equations (GEEs) estimated changes in CD4 cell count in women not receiving ART (other than for prevention of mother-to-child transmission) from the last measurement before pregnancy to the first measurement during pregnancy, from the first measurement during pregnancy to the first measurement after pregnancy, and overall from the last measurement before pregnancy to the first measurement after pregnancy. In this sub-analysis of changes in CD4 cell counts, we included only first pregnancies which began after estimated date of infection.

All analyses were conducted using R 3.2.1 (http://CRAN.R-project.org). All $P$ values are two sided.

RESULTS

Analysis Cohort: Pregnancy Rates and Outcomes

A flow diagram of the analysis cohorts is shown in Figure 1. Two hundred and fifty-five women were enrolled in protocol C (none were on ART at enrollment), and 232 of these women were less than age 40 at estimated date of HIV infection. Seven women with no CD4 data were excluded. Three women had a CD4 set point $<200$ cells/μl leaving 222 women in the clinical progression analysis cohort, and 20 women had a CD4 set point $\leq 350$ cells/μl, leaving 205 women in the immunologic progression analysis cohort.

Among the 222 women included in the clinical progression analysis, 136 pregnancies occurred during 708.6 person-years at risk (19.2/100 person-years at risk). Of the 94 pregnancies resulting in live births, ART for prevention of mother-to-child transmission was reported in 75 (80\%). Pregnancy start and stop dates were imputed based on the algorithm described for seven and 14 pregnancies, respectively. In the clinical progression cohort, 59 women were censored at ART initiation. Pregnancy rates did not differ by clinical progression status ($RR = 1.1$; 95\% CI: 0.7, 1.6).

Among the 205 women included in the immunologic progression analysis, 124 pregnancies occurred during 616.9 person-years at risk (20.1/100 person-years at risk). Of the 85 pregnancies resulting in live births, ART for prevention of mother-to-child transmission was reported in 69 (81\%). Pregnancy start and stop dates were imputed based on the algorithm described for six and 12 pregnancies, respectively. In the immunologic progression cohort, 37 women were censored at the time of ART initiation. Pregnancy rates did not differ by immunologic progression status ($RR = 0.8$; 95\% CI: 0.5, 1.1).
Participant Demographics

We included 222 women with CD4 set point \( \geq 200 \) cells/\( \mu l \) in the clinical progression analysis, and 205 with CD4 set point \( >350 \) cells/\( \mu l \) were included in the immunologic progression analysis. The analysis cohorts were similar, with the exception that the immunologic progression cohort was slightly younger (68% were <30 years old) than the clinical progression cohort (47% were <30 years old). Both clinical and immunologic progressors were older on average than nonprogressors; HLA alleles A*03:01, B*45, and B*57 were relatively rare overall (10%–12% of women), and mean CD4 set point was lower in progressors versus nonprogressors. The majority had subtype C or A infections, and most were from Zambia or Uganda (Table 1).

Clinical Disease Progression Rates, Crude, and Adjusted Associations

Primary Analysis

Sixty-three clinical progressions occurred among 222 women (8.0/100 person-years at risk; 95% CI: 6.2, 10.3). Women who progressed experienced 89 total events: 14 women had CD4 count <200 cells/\( \mu l \) as their only event, 21 had percent CD4 <14% as their only event, five had only a category C event, 18 had both CD4 count <200 cells/\( \mu l \) and percent CD4 <14%, two had a percent CD4 <14% and a category C event, and three experienced all three events. During pregnancy, women had a lower rate of progression in unadjusted (crude hazard ratio, cHR = 0.7; 95% CI: 0.3, 1.9) and adjusted (aHR = 0.7, 95% CI: 0.2, 1.8) analyses, although the confidence intervals are wide (Table 2).

Sensitivity Analysis

With ART initiation (other than for prevention of mother-to-child transmission) included in the definition of clinical progression, 122 women progressed (15.6/100 person-years at risk; 95% CI: 12.9, 18.6). Overall, 95 women started ART, 35 had a CD4 count <200 cells/\( \mu l \), 44 had a percent CD4 <14%, and 12 had a category C event. Rates of progress were higher for pregnant (n = 20 progressions, 26.7/100 person-years at risk) versus nonpregnant (n = 102 progressions, 14.4/100 person-years at risk) women in unadjusted (cHR = 2.0; 95% CI: 1.3, 3.2) and adjusted (aHR = 2.1; 95% CI: 1.3, 3.3) analyses.

Immunologic Disease Progression Rates and Crude and Adjusted Associations

Eighty-seven immunologic progressions occurred among 205 women (12.8/100 person-years at risk; 95% CI: 10.3, 15.8). Of these 87 women, 78 had two consecutive CD4 counts of \( \leq 350 \) while nine had a single CD4 \( \leq 350 \) followed by ART initiation (other than for prevention of mother-to-child transmission) before their next CD4 measure. During pregnancy, women had higher rates of immunologic disease progression in unadjusted (cHR = 1.4; 95% CI: 0.8, 2.6) and adjusted (aHR = 1.7; 95% CI: 0.9, 3.3) analyses, although...
One hundred seventeen women had at least one pregnancy during study follow-up; those pregnant at their estimated date of HIV infection (n = 23) and using ART before CD4 measurements (n = 16) were excluded.

For the remaining 78 ART-naive women (Figure 2), CD4 count declined 74 cells/µl (95% CI: −4, 152) from the last count before pregnancy to the first count during pregnancy. CD4 count rebounded 40 cells/µl (95% CI: −38 to 118) from the first count during pregnancy to the first count after pregnancy (58 cells/µl among those reporting therapy for prevention of mother-to-child transmission and 27 cells/µl for those not reporting preventive therapy). CD4 counts measured before pregnancies began versus after pregnancies ended (over an average of 348 days [range 76–560 days]) were not different.

**DISCUSSION**

In this multinational early HIV infection cohort in Africa, we found that pregnancy was not associated with clinical or immunologic HIV disease progression in primary analyses, that CD4 counts rebounded after pregnancy ended, and that overall decreases in CD4 counts were small. However, in sensitivity analyses, we saw an increase in clinical progression when ART initiation (other than for prevention of mother-to-child transmission) was included in that outcome. Overall, these findings are supportive of those from several meta-analyses and individual studies1,14,26,27,32–34 and are in contrast to relatively few studies14,25; however, disparate outcome measures make direct comparisons challenging.

In our primary analysis of clinical progression, we found a protective effect for pregnancy (aHR = 0.7). This is similar to a study among 303 HIV-infected women from Uganda.
### TABLE 2. Clinical Progression Outcome Rates, Crude HRs, and Adjusted HRs (N = 222)

<table>
<thead>
<tr>
<th>Pregnancy status</th>
<th>No. Outcomes (Total N = 63)</th>
<th>PY at Risk (Total PY = 783.5)</th>
<th>Outcome Rate/100 PY (95% CI)</th>
<th>Unadjusted Analysis</th>
<th>Adjusted Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>eHR (95% CI)</td>
<td>aHR (95% CI)</td>
</tr>
<tr>
<td>No</td>
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<td>708.6</td>
<td>8.3 (6.3, 10.7)</td>
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<td>Ref</td>
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</tr>
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<td>&lt;30</td>
<td>37</td>
<td>521.3</td>
<td>7.1 (5.0, 9.8)</td>
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<td>≥30</td>
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<td>690.8</td>
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<td>0.7 (0.6, 0.9)</td>
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<td>A</td>
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<td>6.8 (1.8, 17.3)</td>
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EDI indicates estimated date of infection; PY, person-year; RSA, Republic of South Africa.

and Zimbabwe recruited immediately after seroconversion by Morrison et al., which found a protective association between pregnancy and time to AIDS (aHR = 0.19; 95% CI: 0.03, 1.33), defining AIDS as CD4 count ≤200 cells/μl or WHO clinical stage 4 disease or severe stage 3 disease, similar to the definition used in our primary analysis. These findings may be explained as the “healthy pregnant woman” (the concept that women who achieve pregnancy are generally healthier than women who do not) effect or improved frequency or quality of care that pregnant women may receive. We do not feel that this effect could be largely contributed to prevention of mother-to-child transmission use, as CD4 counts decrease during pregnancy even among prevention of mother-to-child transmission users, we see an increased rate of immunological progression during pregnancy even among prevention of mother-to-child transmission users, and prevention of mother-to-child transmission was generally given near the time of delivery.

The definition of clinical progression in our sensitivity analysis is more similar to that used by Heffron et al., (ART initiation, a single CD4 <200, and/or nontraumatic death). The study by Heffron et al., found increased progression risk during pregnancy (aHR = 1.45; 95% CI: 1.03, 2.04), and 73 (20%) of progressions were classified solely due to ART initiation. In our study, 59 (48%) progressions were classified solely due to ART initiation (other than for prevention of mother-to-child transmission). Since women who become pregnant are more likely to be offered and receive ART independent of CD4 count or stage of disease (likely due in part to the roll-out of Option B+), ART initiation is not measuring the same constructs as death or immunologic progression. We recommend that composite outcomes including ART initiation be cautiously interpreted, and that future studies model composite outcomes both with and without ART initiation.

We found a moderately increased hazard of immunologic HIV disease progression among pregnant women (aHR = 1.7), possibly due in part to normal changes in the immune system and hemodilution experienced during pregnancy. Importantly, and similar to a study of 2269 chronically HIV-infected
ART-naive women from five African countries, we found that although average CD4 counts dropped during pregnancy relative to nonpregnant intervals, those declines were small. Furthermore, the magnitude of these changes overall is likely of minimal clinical significance, regardless of use of ART for prevention of mother-child transmission.

Other covariates examined previously in the larger multicenter cohort were also of interest. We found that HLA A*03:01 and B*57 alleles were associated with protection from progression while HLA B*45 was associated with increased risk. In the larger cohort analysis, HLA A*03:01 was strongly associated with low viral load in women but not men among 521 recent seroconverters. The B*45 allele was a risk factor for immunologic or virologic disease progression regardless of gender. In addition, B*57 was associated with lower disease progression in the full cohort with no sex-specific interaction between this allele and viral load. However, as in the larger cohort study, these findings should be interpreted with caution given the small number of persons carrying these alleles. Also similar to the larger cohort, we found women with HIV subtype C or D experienced faster immunologic progression relative to subtype A.

Pregnancy incidence did not differ meaningfully by country and was similar to other recent, multicountry African cohort studies indicating that HIV-infected African women are having increasingly more children. Of course, pregnancy indicates a lack of condom use among HIV-infected women and the potential for HIV transmission to partners who are HIV negative.

As with all observational studies, limitations include the possibility of unmeasured confounding. We did not explore other clinical and immunologic measures of disease progression; for example, we did not have sufficient outcomes to consider death (n = 9). In the systematic review by Calvert and Ronsmans, pregnancy was associated with HIV-related death among HIV-infected non-ART users in women in five studies (summary pooled RR = 1.65; 95% CI: 1.06, 2.57) although the single study from an African cohort did not find an association with time to HIV-related death in Rwandan women (aHR = 0.96; 95% CI: 0.48, 1.93). Similarly, a study from Zambia published after this meta-analysis found no association between time-varying

### TABLE 3. Immunologic Progression Outcome Rates, Crude HRs, and Adjusted HRs (N = 205)

<table>
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<tr>
<th>Pregnancy Status</th>
<th>No. Outcomes (Total N = 87)</th>
<th>PY at Risk (Total PY = 680.1)</th>
<th>Outcome Rate/100 PY (95% CI)</th>
<th>Unadjusted Analysis</th>
<th>Adjusted Analysis</th>
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<td>10%</td>
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</table>

**EDI** indicates estimated date of infection; **PY**, person-year; **RSA**, Republic of South Africa.
pregnancy and all-cause mortality (the majority of which was HIV related) (aHR = 1.07; 95% CI: 0.68, 1.66) in non-ART using HIV-infected women. Our study was relatively small and, similar to other studies, had limited power to detect differences in disease progression by pregnancy; however, we were able to estimate a relatively precise date of infection giving us robust estimates of duration of infection. The imputation of a small number of pregnancy start and end dates could lead to misclassification of the timing of the exposure, while the spacing of study visits could lead to misclassification of the timing of the outcome; however, temporality between exposure and outcome was always maintained. We did not have a measure of breastfeeding collected consistently across all study sites and therefore could not explore the effect of breastfeeding on disease progression, nor could we use breastfeeding intervals to further refine the person-time at risk excluded when calculating pregnancy rates.

Except in Kenya, ART use was self-reported, which could lead to misclassification of the outcome used in sensitivity analyses (again, we note that because women who become pregnant are more likely to receive ART independent of disease progression, use of ART initiation as a proxy measure of disease progression suffers from confounding my indication). Finally, we are not examining the effect of cumulative pregnancy history on disease progression, which is also of clinical and public health importance, but rather risk imparted due to current pregnancy.

**CONCLUSIONS**

In this study of African women in an early HIV infection cohort from five countries, pregnancy did not appear to increase rates of clinical or immunologic HIV disease progression in the absence of ART (other than prevention of mother-to-child transmission). Deleterious effects of pregnancy on CD4 counts appear small and temporary. These findings indicate that HIV-positive women may become pregnant without increased disease progression. Further evaluation of longer-term impact of pregnancy, and cumulative time pregnant, on clinical and immunologic progression is warranted.

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