

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

Kristin M. Wall,^{a,b} Wasima Rida,^c Lisa B. Haddad,^d Anatoli Kamali,^e Etienne Karita,^f Shabir Lakhi,^g William Kilembe,^g Susan Allen,^a Mubiana Inambao,^h Annie H. Yang,ⁱ Mary H. Latka,^j Omu Anzala,^k Eduard J. Sanders,^{l,m} Linda-Gail Bekker,ⁿ Vinodh A. Edward,^{j,o} and Matt A. Price^{p,q}

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/ μ l, 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 \leq 350 cells/ μ l or a single CD4 \leq 350 cells/ μ l 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.

(*Epidemiology* 2017;28: 224–232)

Submitted 11 January 2016; accepted 14 November 2016.

From the ^aDepartment of Epidemiology, Rollins School of Public Health, Laney Graduate School, Emory University, Atlanta, GA; ^bRwanda Zambia HIV Research Group, Department of Pathology & Laboratory Medicine, School of Medicine and Hubert Department of Global Health and the Department of Epidemiology, Rollins School of Public Health, Laney Graduate School, Emory University, Atlanta, GA; ^cBiostatistics Consultant, Arlington, VA; ^dDepartment of Gynecology and Obstetrics, Emory University, School of Medicine, Atlanta, GA; ^eMedical Research Council/Uganda Virus Research Unit, Research Unit on AIDS, Entebbe, Uganda; ^fRwanda Zambia HIV Research Group, Department of Pathology & Laboratory Medicine, School of Medicine and Hubert Department of Global Health and the Department of Epidemiology, Rollins School of Public Health, Laney Graduate School, Emory University, Kigali, Rwanda; ^gRwanda Zambia HIV Research Group, Department of Pathology & Laboratory Medicine, School of Medicine and Hubert Department of Global Health and the Department of Epidemiology, Rollins School of Public Health, Laney Graduate School, Emory University, Lusaka, Zambia; ^hRwanda Zambia HIV Research Group, Department of Pathology & Laboratory Medicine, School of Medicine and Hubert Department of Global Health and the Department of Epidemiology, Rollins School of Public Health, Laney Graduate School, Emory University, Ndola, Zambia; ⁱDepartment of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; ^jThe Aurum Institute, Johannesburg

and Rustenburg, South Africa; ^kKenya AIDS Vaccine Initiative Institute of Clinical Research, University of Nairobi, Nairobi, Kenya; ^lCentre for Geographic Medicine-Coast/Kenya Medical Research Institute, Kilifi, Kenya; ^mUniversity of Oxford, Oxford, United Kingdom; ⁿDesmond Tutu HIV Centre, University of Cape Town, Cape Town, Republic of South Africa; ^oSchool of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; ^pInternational AIDS Vaccine Initiative, New York, NY; and ^qDepartment of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, CA.

Mary H. Latka is currently at Peace Corps, Santo Domingo, Dominican Republic.

This study was supported by IAVI and made possible by the support of many donors, including the Bill & Melinda Gates Foundation; the Ministry of Foreign Affairs of Denmark; Irish Aid; the Ministry of Finance of Japan in partnership with The World Bank; the Ministry of Foreign Affairs of the Netherlands; the Norwegian Agency for Development Cooperation (NORAD); the United Kingdom Department for International Development (DFID), and the United States Agency for International Development (USAID). The full list of IAVI donors is available at www.iavi.org. This study is made possible by the generous support of the American people through USAID. The contents are the responsibility of the International AIDS Vaccine Initiative and do not necessarily reflect the views of USAID or the United States Government. The IAVI Africa HIV Prevention Partnership includes: Mary Mwangome (KEMRI), Elizabeth Wahome (KEMRI), Gwynn Stevens (IAVI), Pontiano Kaleebu (MRC/UVRI), Heeran Makkan (AI), Gaudensia Mutua (KAVI), Eugene Ruzagira (MRC), Ubaldo Bahe-muka (MRC), Rogers Twesigye (MRC), Agnes Bwanika (MRC), Freddie Kibengo (MRC), Roger Bayingana (PSF), Eric Hunter (PSF, ZEHHP, Emory University), Mubiana Inambao (ZEHHP), Kayitesi Kayitenkore (PSF).

The authors report no conflicts of interest.

Correspondence: Kristin M. Wall, 1518 Clifton Road NE, Atlanta, GA 30322. E-mail: kmwall@emory.edu.

Copyright © 2016 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CC BY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 1044-3983/17/2802-0224

DOI: 10.1097/EDE.0000000000000590

The effect of pregnancy on HIV disease progression has been a topic of debate and uncertainty for over two decades.¹ This is an issue of increasing importance since, with advances in HIV treatment, care, and prevention of mother-to-child transmission, pregnancy incidence^{2–6} and desire for children^{6–9} among HIV-infected African women are increasing while rates of unintended pregnancy remain high.^{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-analysis¹⁴ 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^{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).²⁴ 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).¹⁹ The review also found pregnancy was marginally associated with decreasing CD4 cell counts among HIV+ non-ART using women in four studies^{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/ μ l in Ugandan women (aHR = 1.67; 95% CI: 0.77, 3.63).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/ μ l, ART initiation, or nontraumatic death (aHR = 1.45; 95% CI: 1.03, 2.04).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),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).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.^{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 <200 cells/ μ l, 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/ μ l. Category C events were defined per CDC and WHO guidelines.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/ μ l or a single CD4 count \leq 350 cells/ μ l 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/ μ l.

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.³¹ 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/ μ l leaving 222 women in the clinical progression analysis cohort, and 20 women had a CD4 set point \leq 350 cells/ μ l, 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).

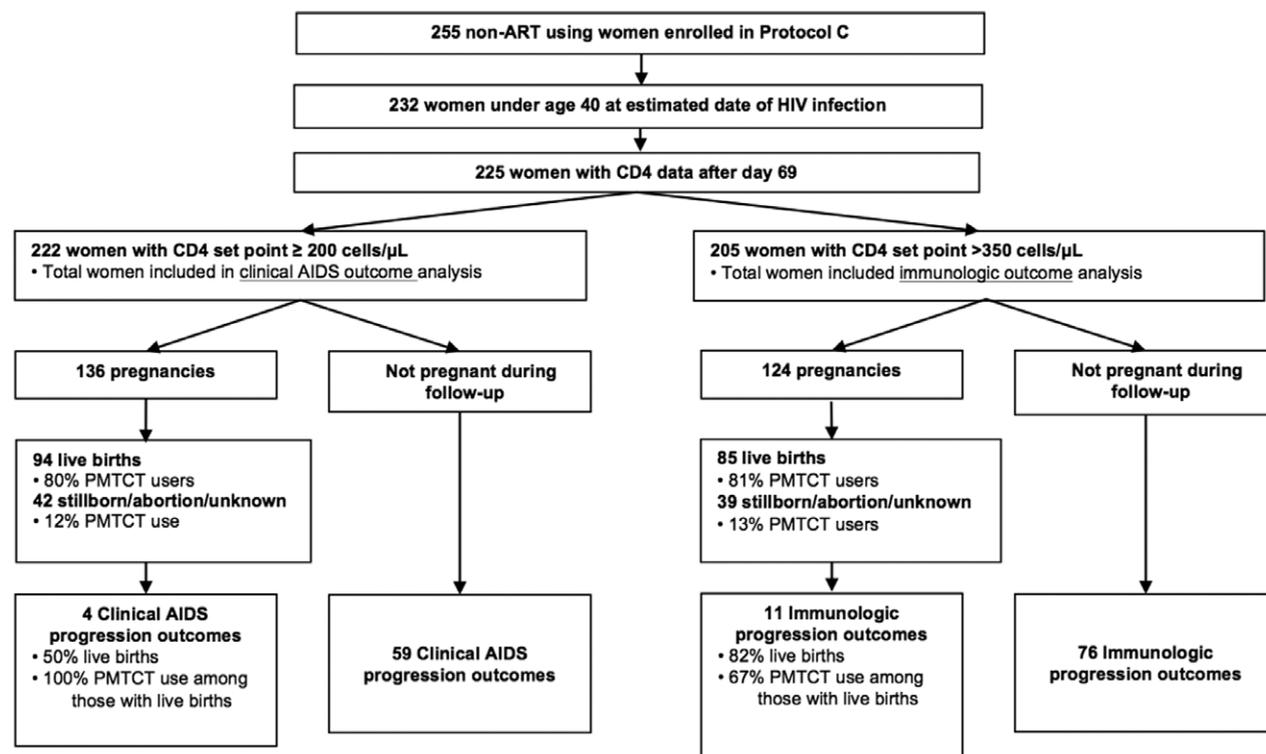


FIGURE 1. Study flow diagram.

Participant Demographics

We included 222 women with CD4 set point ≥ 200 cells/ μL in the clinical progression analysis, and 205 with CD4 set point >350 cells/ μL 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/ μL 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/ μL 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/ μL , 44 had a percent CD4 $<14\%$, and 12 had a category C event. Rates of progression 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 ≤ 350 while nine had a single CD4 ≤ 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

TABLE 1. Characteristics of Women in an Early HIV Infection Cohort at Enrollment by Disease Progression Outcomes

	Total in Clinical Progression Outcome Analysis (N = 222)	Clinical Progressors (N = 63)	Nonclinical Progressors (N = 159)	Total in Immunologic Progression Outcome Analysis (N = 205)	Immunologic Progressors (N = 87)	Nonimmunologic Progressors (N = 118)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Age at EDI						
<30 years	152 (47)	37 (59)	115 (44)	139 (68)	52 (60)	87 (74)
≥30 years	170 (53)	26 (41)	144 (56)	66 (32)	35 (40)	31 (26)
HLA A*03:01 allele						
No	194 (89)	58 (92)	136 (88)	178 (89)	82 (94)	96 (84)
Yes	24 (11)	5 (8)	19 (12)	23 (11)	5 (6)	18 (16)
HLA B*45 allele						
No	191 (88)	54 (86)	137 (88)	179 (89)	74 (85)	105 (92)
Yes	27 (12)	9 (14)	18 (12)	22 (11)	13 (15)	9 (8)
HLA B*57 allele						
No	196 (90)	61 (97)	135 (87)	181 (90)	81 (93)	100 (88)
Yes	22 (10)	2 (3)	20 (13)	20 (10)	6 (7)	14 (12)
CD4 set point (cells/ml, mean, SD)	634 (260)	542 (238)	671 (260)	664 (248)	567 (183)	735 (265)
HIV-1 subtype						
A	65 (29)	17 (27)	48 (30)	62 (30)	22 (25)	40 (34)
C	115 (52)	31 (49)	84 (53)	108 (53)	50 (57)	58 (50)
D	34 (15)	11 (17)	23 (15)	29 (14)	14 (16)	15 (13)
Other	7 (3)	4 (6)	3 (2)	5 (2)	1 (1)	4 (3)
Country						
Zambia	91 (41)	28 (44)	63 (40)	87 (42)	43 (49)	44 (37)
Uganda	58 (26)	19 (30)	39 (25)	50 (24)	17 (20)	33 (28)
Rwanda	37 (17)	9 (14)	28 (18)	37 (18)	17 (20)	20 (17)
RSA	22 (10)	3 (5)	19 (12)	18 (9)	6 (7)	12 (10)
Kenya	14 (6)	4 (6)	10 (6)	13 (6)	4 (5)	9 (8)

EDI indicates estimated date of infection; RSA, Republic of South Africa.

again confidence intervals were wide. In adjusted analyses, women with HLA allele A*03:01 and B*57 experienced lower rates of progression, while those with HLA B*45 experienced higher rates. For every 100 cells/μl increase in CD4 set point, the hazard of progression decreased by 34%. Women with subtype C or D progressed faster than women with subtype A (Table 3).

CD4 Count Before, During, and After Pregnancy

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-naïve 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 studies^{1,14,26,27,32–34} and are in contrast to relatively few studies^{14,25}; 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)

	No. Outcomes (Total N = 63)	PY at Risk (Total PY = 783.5)	Outcome Rate/100 PY (95% CI)	Unadjusted Analysis	Adjusted Analysis
				cHR (95% CI)	aHR (95% CI)
Pregnancy status					
No	59	708.6	8.3 (6.3, 10.7)	Ref	Ref
Yes	4	74.9	5.3 (1.5, 13.7)	0.7 (0.3, 1.9)	0.7 (0.2, 1.8)
Age at EDI (years)					
<30	37	521.3	7.1 (5.0, 9.8)	Ref	Ref
≥30	26	262.1	9.9 (6.5, 14.5)	1.4 (0.9, 2.3)	1.5 (0.9, 2.5)
HLA A*03:01 allele					
No	58	674.5	8.6 (6.5, 11.1)	Ref	Ref
Yes	5	100.9	5.0 (1.6, 11.6)	0.6 (0.2, 1.6)	0.7 (0.2, 1.9)
HLA B*45 allele					
No	54	711.3	7.6 (5.7, 9.9)	Ref	Ref
Yes	9	64.0	14.1 (6.4, 26.7)	1.8 (0.8, 3.8)	1.7 (0.8, 3.7)
HLA B*57 allele					
No	61	690.8	8.8 (6.8, 11.3)	Ref	Ref
Yes	2	84.6	2.4 (0.3, 8.5)	0.3 (0.1, 1.0)	0.3 (0.1, 1.0)
CD4 set point (per 100 cells/ml increase)	W			0.7 (0.6, 0.9)	0.7 (0.6, 0.9)
HIV-1 subtype					
A	17	262.2	6.5 (3.8, 10.4)	Ref	Ref
C	31	393.6	7.9 (5.4, 11.2)	1.2 (0.7, 2.1)	1.0 (0.5, 1.8)
D	11	107.4	10.2 (5.1, 18.3)	1.5 (0.7, 3.4)	1.4 (0.6, 3.3)
Other	4	14.3	27.9 (7.6, 71.6)	3.9 (1.6, 9.3)	3.0 (1.3, 6.9)
Country					
Zambia	28	318.0	8.8 (5.9, 12.7)	Ref	
Uganda	19	190.9	10.0 (6.0, 15.5)	1.2 (0.6, 2.1)	
Rwanda	9	156.0	5.8 (2.6, 11.0)	0.7 (0.3, 1.5)	
RSA	3	59.4	5.1 (1.0, 14.8)	0.6 (0.2, 1.9)	
Kenya	4	59.3	6.8 (1.8, 17.3)	0.8 (0.3, 2.3)	

EDI indicates estimated date of infection; PY, person-year; RSA, Republic of South Africa.

and Zimbabwe recruited immediately after seroconversion by Morrison et al.²⁷ 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.²⁵ (ART

initiation, a single CD4 <200, and/or nontraumatic death). The study by Heffron et al.²⁵ 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.³⁶ Importantly, and similar to a study of 2269 chronically HIV-infected

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

	No. Outcomes (Total N = 87)	PY at Risk (Total PY = 680.1)	Outcome Rate/100 PY (95% CI)	Unadjusted Analysis	Adjusted Analysis
				cHR (95% CI)	aHR (95% CI)
Pregnancy status					
No	76	616.9	12.3 (9.7, 15.4)	Ref	Ref
Yes	11	63.2	17.4 (8.7, 31.1)	1.4 (0.8, 2.6)	1.7 (0.9, 3.3)
Age at EDI (years)					
<30	52	459.8	11.3 (8.5, 14.8)	Ref	Ref
≥30	35	220.3	15.9 (11.1, 22.1)	1.4 (0.9, 2.2)	1.6 (1.0, 2.5)
HLA A*03:01 allele					
No	82	577.8	14.2 (11.3, 17.6)	Ref	Ref
Yes	5	96.9	5.2 (1.7, 12.0)	0.4, (0.1, 0.9)	0.3 (0.1, 0.8)
HLA B*45 allele					
No	74	627.4	11.8 (9.3, 14.8)	Ref	Ref
Yes	13	47.3	27.5 (14.6, 47.0)	1.7 (1.0, 3.0)	2.1 (1.1, 3.9)
HLA B*57 allele					
No	81	610.3	13.3(10.5, 16.5)	Ref	Ref
Yes	6	64.3	9.3 (3.4, 20.3)	0.6 (0.3, 1.4)	0.5 (0.2, 1.2)
CD4 set point (per 100 cells/ml increase)	-	-	-	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)
HIV-1 subtype					
A	22	241.2	9.1 (5.7, 13.8)	Ref	Ref
C	50	320.0	15.6 (11.6, 20.6)	1.7 (1.1, 2.8)	1.7 (1.0, 2.8)
D	14	103.2	13.6 (7.4, 22.8)	1.5 (0.8, 2.9)	2.0 (1.0, 4.1)
Other	1	9.8	10.2 (0.3, 56.9)	1.2 (0.2, 7.2)	0.8 (0.1, 6.0)
Country					
Zambia	43	249.4	17.2 (12.5, 23.2)	Ref	
Uganda	17	185.8	9.2 (5.3, 14.7)	0.5 (0.3, 0.9)	
Rwanda	17	149.7	11.4 (6.6, 18.2)	0.7 (0.4, 1.1)	
RSA	6	45.2	13.3 (4.9, 28.9)	0.8 (0.3, 1.9)	
Kenya	4	50.1	8.0 (2.2, 20.4)	0.5 (0.2, 1.4)	

EDI indicates estimated date of infection; PY, person-year; RSA, Republic of South Africa.

ART-naïve women from five African countries,³⁴ 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.³⁷ The B*45 allele was a risk factor for immunologic or virologic disease progression regardless of gender.^{28,37} In addition, B*57 was associated with lower disease progression in the full cohort²⁸ with no sex-specific interaction between this allele and viral load.³⁷ 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.²⁸

Pregnancy incidence did not differ meaningfully by country and was similar to other recent, multicountry African cohort studies^{34,38} indicating that HIV-infected African women are having increasingly more children.^{2-7,38} 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,¹⁴ pregnancy was associated with HIV-related death among HIV-infected non-ART using women in five studies^{16,17,33,39} (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).³³ Similarly, a study from Zambia published after this meta-analysis⁴⁰ found no association between time-varying

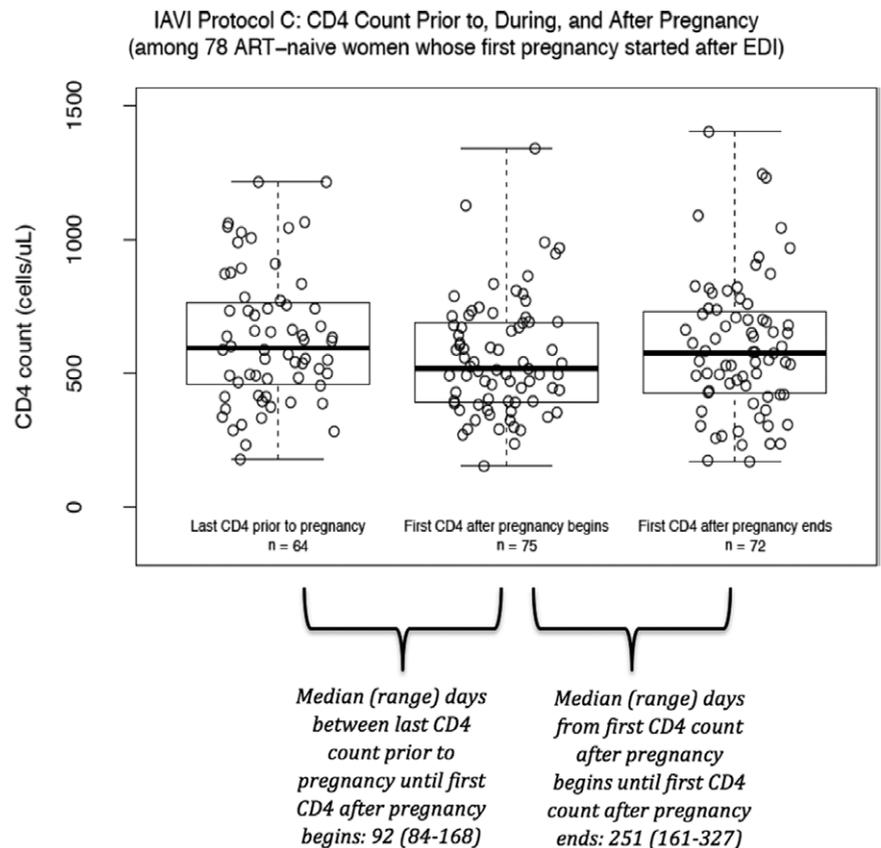


FIGURE 2. CD4 count among N = 78 ART naïve women during their first pregnancy after estimated date of HIV infection.

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 by 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.

ACKNOWLEDGMENTS

The authors are grateful to numerous people, whose contributions have made this study possible: All of the study participants, Drs. James Tang and Richard Kaslow (University of Alabama at Birmingham for HLA typing), Dr. Ed Acosta (University of Alabama at Birmingham School of Medicine for antiretroviral drug testing), staff at the Central Laboratory Services and the Perinatal HIV Research Unit, South Africa; staff at the IAVI Human Immunology Laboratory, Imperial College, London; the Africa-based IAVI staff; Helen Thomson, Marietta Krebs, Leslie Nielsen, Melissa Simek, Lisa Stoll, Paul Sayer, Jan de Bont, Andrea von Lieven, Sarah Yates, Elise van der Elst, Dr. Nzeera Ketter, Dr. Chrispin Kambili, and Dr. Pauli Amornkul. We also thank the study funders: Becton, Dickinson and Company;

Bill and Melinda Gates Foundation; Bristol-Meyers Squibb; Canadian International Development Agency; Dutch Product Development Partnership Fund; European Commission South Africa; Foundation for the National Institute of Health; John Evans Foundation; Medical Research Council; Norwegian Agency for Development Corporation; Organization of the Petroleum Exporting Countries (OPEC) Fund for International Development; Pfizer, Inc.; Spain Ministry of Foreign Affairs; Swedish International Development Agency; United Kingdom Department for International Development; United States Agency for International Development (USAID); and World Bank.

REFERENCES

- French R, Brocklehurst P. The effect of pregnancy on survival in women infected with HIV: a systematic review of the literature and meta-analysis. *Br J Obstet Gynaecol.* 1998;105:827–835.
- Guthrie BL, Choi RY, Bosire R, et al. Predicting pregnancy in HIV-1 discordant couples. *AIDS Behav.* 2010;14:1066–1071.
- Heffron R, Were E, Celum C, et al.; Partners in Prevention HSV/HIV Transmission Study Team. A prospective study of contraceptive use among African women in HIV-1 serodiscordant partnerships. *Sex Transm Dis.* 2010;37:621–628.
- Schwartz SR, Rees H, Mehta S, Venter WD, Taha TE, Black V. High incidence of unplanned pregnancy after antiretroviral therapy initiation: findings from a prospective cohort study in South Africa. *PLoS One.* 2012;7:e36039.
- Taulo F, Berry M, Tsui A, et al. Fertility intentions of HIV-1 infected and uninfected women in Malawi: a longitudinal study. *AIDS Behav.* 2009;13 Suppl 1:20–27.
- Kabami J, Turyakira E, Biraro S, Bajunirwe F. Increasing incidence of pregnancy among women receiving HIV care and treatment at a large urban facility in western Uganda. *Reprod Health.* 2014;11:81.
- Homsy J, Bunnell R, Moore D, et al. Reproductive intentions and outcomes among women on antiretroviral therapy in rural Uganda: a prospective cohort study. *PLoS One.* 2009;4:e4149.
- Kaida A, Laher F, Strathdee SA, et al. Childbearing intentions of HIV-positive women of reproductive age in Soweto, South Africa: the influence of expanding access to HAART in an HIV hyperendemic setting. *Am J Public Health.* 2011;101:350–358.
- Matthews LT, Crankshaw T, Giddy J, et al. Reproductive decision-making and periconception practices among HIV-positive men and women attending HIV services in Durban, South Africa. *AIDS Behav.* 2013;17:461–470.
- Obare F, van der Kwaak A, Birungi H. Factors associated with unintended pregnancy, poor birth outcomes and post-partum contraceptive use among HIV-positive female adolescents in Kenya. *BMC Womens Health.* 2012;12:34.
- Wall KM, Kilembe W, Vwalika B, et al. Hormonal contraception does not increase women's HIV acquisition risk in Zambian discordant couples, 1994–2012. *Contraception.* 2015;91:480–487.
- Wall KM, Haddad L, Vwalika B, et al. Unintended pregnancy among HIV positive couples receiving integrated HIV counseling, testing, and family planning services in Zambia. *PLoS One.* 2013;8:e75353.
- King R, Khana K, Nakayiwa S, et al. 'Pregnancy comes accidentally—like it did with me': reproductive decisions among women on ART and their partners in rural Uganda. *BMC Public Health.* 2011;11:530.
- Calvert C, Ronsmans C. Pregnancy and HIV disease progression: a systematic review and meta-analysis. *Trop Med Int Health.* 2015;20:122–145.
- Alliegre MB, Dorrucchi M, Phillips AN, et al. Incidence and consequences of pregnancy in women with known duration of HIV infection. Italian Seroconversion Study Group. *Arch Intern Med.* 1997;157:2585–2590.
- Berrebi A, Kobuch WE, Puel J, et al. Influence of pregnancy on human immunodeficiency virus disease. *Eur J Obstet Gynecol Reprod Biol.* 1990;37:211–217.
- Deschamps MM, Pape JW, Desvarieux M, et al. A prospective study of HIV-seropositive asymptomatic women of childbearing age in a developing country. *J Acquir Immune Defic Syndr.* 1993;6:446–451.
- Hocke C, Morlat P, Chene G, Dequae L, Dabis F. Prospective cohort study of the effect of pregnancy on the progression of human immunodeficiency virus infection. The Groupe d'Epidémiologie Clinique Du SIDA en Aquitaine. *Obstet Gynecol.* 1995;86:886–891.
- Lieve VD, Shafer LA, Mayanja BN, Whitworth JA, Grosskurth H. Effect of pregnancy on HIV disease progression and survival among women in rural Uganda. *Trop Med Int Health.* 2007;12:920–928.
- Weisser M, Rudin C, Battegay M, Pfluger D, Kully C, Egger M. Does pregnancy influence the course of HIV infection? Evidence from two large Swiss cohort studies. *J Acquir Immune Defic Syndr Hum Retroviro.* 1998;17:404–410.
- Bessinger R, Clark R, Kissinger P, Rice J, Coughlin S. Pregnancy is not associated with the progression of HIV disease in women attending an HIV outpatient program. *Am J Epidemiol.* 1998;147:434–440.
- Buskin SE, Diamond C, Hopkins SG. HIV-infected pregnant women and progression of HIV disease. *Arch Intern Med.* 1998;158:1277–1278.
- Saada M, Le Chenadec J, Berrebi A, et al. Pregnancy and progression to AIDS: results of the French prospective cohorts. SEROGEST and SEROCO Study Groups. *AIDS.* 2000;14:2355–2360.
- Tai JH, Udoji MA, Barkanic G, et al. Pregnancy and HIV disease progression during the era of highly active antiretroviral therapy. *J Infect Dis.* 2007;196:1044–1052.
- Heffron R, Mugo N, Ngure K, et al.; Partners in Prevention HSV/HIV Transmission Study Team. Hormonal contraceptive use and risk of HIV-1 disease progression. *AIDS.* 2013;27:261–267.
- Polis CB, Wawer MJ, Kiwanuka N, et al. Effect of hormonal contraceptive use on HIV progression in female HIV seroconverters in Rakai, Uganda. *AIDS.* 2010;24:1937–1944.
- Morrison CS, Chen PL, Nankya I, et al. Hormonal contraceptive use and HIV disease progression among women in Uganda and Zimbabwe. *J Acquir Immune Defic Syndr.* 2011;57:157–164.
- Amornkul PN, Karita E, Kamali A, et al.; IAVI Africa HIV Prevention Partnership. Disease progression by infecting HIV-1 subtype in a seroconverter cohort in sub-Saharan Africa. *AIDS.* 2013;27:2775–2786.
- Kamali A, Price MA, Lakhi S, et al.; IAVI Africa HIV Prevention Partnership. Creating an African HIV clinical research and prevention trials network: HIV prevalence, incidence and transmission. *PLoS One.* 2015;10:e0116100.
- AETC National Resource Center. HIV Classification: CDC and WHO Staging Systems. Available at: <http://aidsetc.org/guide/hiv-classification-cdc-and-who-staging-systems>. Accessed August 18, 2015.
- Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 Infection. *N Engl J Med.* 2011;364:1943–1954.
- MacCarthy S, Laher F, Nduna M, Farlane L, Kaida A. Responding to her question: a review of the influence of pregnancy on HIV disease progression in the context of expanded access to HAART in sub-Saharan Africa. *AIDS Behav.* 2009;13(suppl 1):66–71.
- Allen S, Stephenson R, Weiss H, et al. Pregnancy, hormonal contraceptive use, and HIV-related death in Rwanda. *J Womens Health (Larchmt).* 2007;16:1017–1027.
- Heffron R, Donnell D, Kiarie J, et al.; Partners in Prevention HSV/HIV Transmission Study. A prospective study of the effect of pregnancy on CD4 counts and plasma HIV-1 RNA concentrations of antiretroviral-naïve HIV-1-infected women. *J Acquir Immune Defic Syndr.* 2014;65:231–236.
- WHO. Programmatic Update: Use of Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants. Available at: http://www.who.int/hiv/PMTCT_update.pdf Accessed September 9, 2015.
- Watanabe M, Iwatani Y, Hidaka Y, Mitsuda N, Amino N. Changes in soluble CD4 and CD8 proteins in healthy pregnant and postpartum women. *Am J Reprod Immunol.* 1996;36:220–227.
- Li X, Price MA, He D, et al.; IAVI Africa HIV Prevention Partnership. Host genetics and viral load in primary HIV-1 infection: clear evidence for gene by sex interactions. *Hum Genet.* 2014;133:1187–1197.
- Myer L, Carter RJ, Katyal M, Toro P, El-Sadr WM, Abrams EJ. Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study. *PLoS Med.* 2010;7:e1000229.
- Kumar RM, Uduman SA, Khurrana AK. Impact of pregnancy on maternal AIDS. *J Reprod Med.* 1997;42:429–434.
- Wall KM, Kilembe W, Haddad L, et al. Hormonal contraception, pregnancy, breastfeeding and risk of HIV disease progression among Zambian women. *J Acquir Immune Defic Syndr.* 2016;71:345–352.