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Research Article

Incidence of Pregnancy after Initiation of Antiretroviral Therapy in South Africa: A Retrospective Clinical Cohort Analysis

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Background. Little is known about rates of incident pregnancy among HIV-positive women initiating highly active antiretroviral therapy (HAART). *Methods*. We conducted a retrospective clinical cohort study among therapy-naïve women ages 18–45 initiating HAART between 1 April 2004 and 30 September 2009 at an adult HAART clinic in Johannesburg, South Africa. We used Poisson regression to characterize rates and rate ratios of pregnancy. *Results*. We evaluated 5,996 women who experienced 727 pregnancies during 14,095 person-years at risk. The overall rate of pregnancy was 5.2 per 100 person-years (95% confidence limits [CL] 4.8, 5.5). By six years, cumulative incidence of first pregnancy was 22.9% (95% CL 20.6%, 25.4%); among women ages 18–25 at HAART initiation, cumulative incidence was 52.2% (95% CL 35.0%, 71.8%). The strongest predictor of incidence of pregnancy was age, with women 18–25 having 13.2 times the rate of pregnancy of women ages 40–45 in adjusted analysis. CD4 counts below 100 and worse adherence to HAART were associated with lower rates of incident pregnancy. *Conclusions*. Women experience high rates of incident pregnancy after HAART initiation. Understanding which women are most likely to experience pregnancy will help planning and future efforts to understand the implications of pregnancy for response to HAART.

1. Introduction

Women of childbearing age bear the largest burden of HIV in sub-Saharan Africa [1, 2]. This is especially true in South Africa, the country with the largest population of HIV-positive individuals in the world [3]. In South Africa, HIV prevalence among young women is three times that among young men [4], and a stabilizing overall prevalence of HIV may actually mask very high HIV incidence rates among rural and urban women in some parts of the country [5].

The overlap between pregnancy and HIV is even more striking, with very high rates of both HIV and pregnancy incidence reported among young women in parts of South Africa [5] and HIV prevalence reaching 40% among pregnant women in some age groups [2–4]. A recent publication reporting on multiple sites across Africa noted high HIV incidence rates among HIV-positive women in many settings, as well as a 70% increased hazard of pregnancy after initiation of highly active antiretroviral therapy (HAART) [6].

With international support to attain universal access to HAART [7] and a growing interest in "treatment-as-prevention" [8], an increasing incidence of pregnancy among women receiving HAART seems inevitable. While there are some limited data from the pre-HAART era about how pregnancy affects rate of HIV disease progression [9], very little is known about how pregnancy affects responses to HAART [10, 11]. Understanding the patterns and risk factors

for incident pregnancy after HAART initiation is therefore of significant concern to planning and management of women in treatment for HIV; this is especially true in South Africa, where there is wide access to HAART and a very large at-risk population of reproductive-age women.

Here, we characterize predictors of incident pregnancy after HAART initiation in the Themba Lethu Clinic, an adult antiretroviral therapy clinic in urban Johannesburg, South Africa.

2. Methods

2.1. Study Population. We analyzed data from the Themba Lethu Clinic (TLC) observational cohort [12], an observational clinical cohort of adults initiating HAART in Johannesburg, South Africa. Since the beginning of the government era of HAART in South Africa on 1 April 2004, the TLC has provided free antiretroviral therapy and (since October 2006) free clinical care to HIV-positive adults. At present, TLC has over 17,000 patients in care and is the largest single clinic providing HAART in South Africa. Here, we studied previously antiretroviral therapy-naïve women from the time of HAART initiation between 1 April 2004 and 30 September 2009 and followed these women until administrative end of followup on 31 March 2010 or the end of care due to dropout, death, or transfer of care to another site. We excluded women with a baseline age over 45 (in whom pregnancy is rare).

First-line HAART in the time period under study was stavudine, lamivudine, and efavirenz. Due to concerns about teratogenicity, women found to be pregnant are typically placed on lopinavir and ritonavir rather than efavirenz or on nevirapine; nonpregnant women with declared pregnancy intention are placed on nevirapine or lopinavir-ritonavir. Adherence was captured from pharmacy records as the cumulative proportion of days in which a woman had access to antiretroviral drugs; this estimate of adherence is an *upper limit* on potential adherence, because drugs can only be taken correctly if they are available.

Additional details of the TLC clinical database, clinic procedures, and outcomes have been described previously [12, 13]; here we note only that clinical data are captured prospectively in the TLC and that accuracy of data entry has been previously validated [12].

2.2. Statistical Analysis. Baseline characteristics of women were described using simple statistics, including chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables. We used discrete time hazards models fit with pooled logistic regression to characterize predictors of incident pregnancy.

The main outcome in this study was pregnancy after baseline of HAART initiation, hereafter incident pregnancy. We studied all pregnancies recorded in the database, allowing women to have multiple pregnancies; women became at risk of a new pregnancy at the end of a previous pregnancy (including baseline prevalent pregnancy).

Rates and relative rates of pregnancy were estimated using univariate and multivariate Poisson regression, accounting for repeated outcomes using a robust variance estimator. Multivariate analysis of predictors of pregnancy considered baseline measures of employment, history of smoking, and pregnancy, and time-updated measures of age, HAART regimen, body mass index, hemoglobin, CD4 count, viral load, and adherence. In addition, we investigated the effect of baseline employment status and a baseline history of smoking on incidence of pregnancy, but neither strongly predicted pregnancy and so were omitted from final models. Cumulative incidence curves for first pregnancy (only) were estimated using extended Kaplan-Meier estimators.

3. Results

3.1. Population. The initial study population comprised 5,996 women who contributed a total of 175,795 person-months (14,650 person-years) of followup until death, dropout, or end of followup. Person-time at risk for new incident pregnancy (i.e., subtracting person-time experienced during a pregnancy) was 169,138 person-months (14,095 person-years).

Of the 5,996 women, 586 (10%) were pregnant at baseline. Systematic differences between those women pregnant at baseline and those nonpregnant at baseline have been documented elsewhere; generally women who were pregnant at baseline are younger and healthier than those who are nonpregnant at baseline (and are initiating HAART entirely because they are sick) [11]. We review select baseline characteristics of women by baseline pregnancy status in Table 1.

3.2. Incidence of Pregnancy. There were 727 incident pregnancies experienced in the total population; 612 women experienced one pregnancy, 50 women experienced two pregnancies, and 5 women experienced three pregnancies during followup. Of the 727 incident pregnancies, 85 (12%) were among women pregnant at baseline. Among all women, the overall crude rate of incident pregnancy was 5.2 per 100 person-years (95% confidence limits (CLs) 4.8, 5.5 per 100 person-years). Figure 1 shows cumulative incidence of first pregnancy among all women remaining alive and in care, and at risk, during followup; by six years, estimated cumulative incidence of first pregnancy was 22.9% (95% CL 20.6%, 25.4%). The estimated cumulative incidence of pregnancy among women who were between 18 and 25 years old was 52.2% (95% CL 35.0%, 71.8%) by six years of followup.

The median time from HAART initiation to first pregnancy was 14 months (interquartile range (IQR) 7, 26) among women nonpregnant at baseline and 18 months (IQR 10, 28) among those pregnant at baseline. Median time from end of first incident pregnancy to second incident pregnancy among the 55 second pregnancies was 10 months (IQR 5–16). The five observed third pregnancies happened at 4, 10, 12, 18, and 24 months after the end of the second pregnancy.

Table 1: Characteristics of 5,996 women initiating HAART in Johannesburg, South Africa from 1 April 2004 to 30 September 2009 by pregnancy status at baseline.

Baseline characteristics	Pregnant ($n = 586$)	Not pregnant ($n = 5{,}410$)	P-value
Age (years)	30 (26, 33)	34 (29, 38)	<0.0001
Weight (kg)	68 (60, 77)	57 (49, 65)	<0.0001
Body mass index (kg/m^2)	26.5 (23.3, 29.7)	22.2 (19.5, 25.5)	<0.0001
WHO stage III or IV	100 (18.2)	2372 (43.1)	<0.0001
Hemoglobin, low‡	123 (30.9)	2918 (54.7)	<0.0001
CD4 count (cells/mm^3)	156 (106, 200)	93 (35, 164)	<0.0001
CD4 count ≤ 50 (cells/mm^3)	45 (8.8)	1739 (32.6)	<0.0001

Categorical variables are expressed as number (% total); continuous variables are expressed as median (interquartile range). P-values are two-sided by chi-square test or Wilcoxon rank sum test. ‡After adjustment for altitude, lower limit of normal hemoglobin is 11.35 and 10.35 g/dL for nonpregnant and pregnant women, respectively.

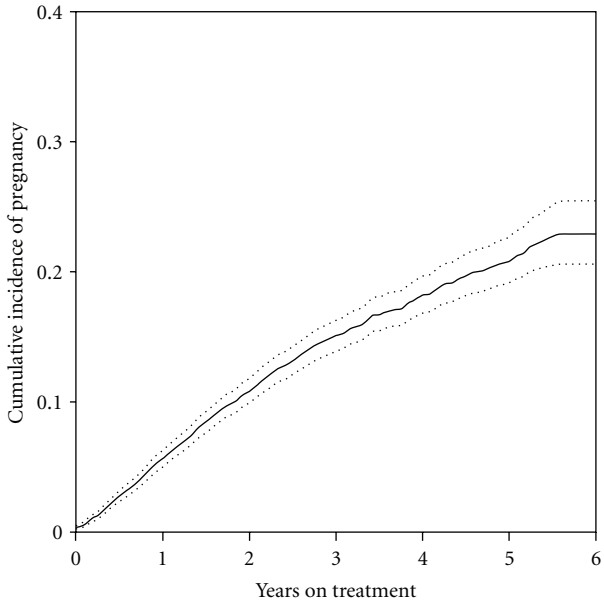

Figure 1: Cumulative incidence of first pregnancy among 5,996 women initiating HAART in Johannesburg, South Africa, from time of HAART initiation, with 95% confidence bounds.

3.3. Characteristics of Incident Pregnancies. Among women who became pregnant, median (interquartile range (IQR)) age at first pregnancy was 31.5 (28.1, 34.7). Age at second pregnancy (among the 55 women who experienced a second pregnancy) was 31.0 (28.2, 35.5). The plurality of pregnancies ($n = 281$) occurred in women ages 30–35, but rate of pregnancy was highest among 18–25-year olds at 10.4 (95% CL 8.2, 13.3) per 100 person-years to 0.9 (95% CL 0.6, 1.3) per 100 person-years among 40–45-year olds in this population (Table 2).

The median CD4 count at first pregnancy was 314 (IQR 193, 448) cells/mm^3, with a mean of 338 cells/mm^3. At second pregnancy, median CD4 count was 377 (IQR 305, 515) cells/mm^3 with a mean of 427 cells/mm^3. The majority of pregnancies ($n = 223$) occurred in women with CD4 200–350 cells/mm^3, while only 18 happened in women with CD4 ≤ 50 cells/mm^3. Rates of pregnancy were highest in women with CD4 counts between 350 and 500 cells/mm^3 (Table 2).

Body mass index (BMI) was similar at time of first and second pregnancy; overall, median BMI was 24.8 (IQR 21.9, 27.7) kg/m^2 at time of any incident pregnancy, with a mean of 25.5 kg/m^2. About half of pregnancies ($n = 348$) occurred in women with BMI 18.5–25.0 kg/m^2. Rates of pregnancy were highest in women with BMI between 25 and 30 kg/m^2 (Table 2).

The majority of incident pregnancy occurred while exposed to efavirenz ($n = 522$, 72% of all pregnancies); of these, about 75% switched away from efavirenz within the term of the pregnancy. Among the remaining pregnancies, approximately equal proportions were exposed to nevirapine and lopinavir-ritonavir. Rates of pregnancy were highest among women receiving nevirapine (Table 2).

3.4. Predictors of Incident Pregnancy. In this population, incident pregnancy was more common among younger, healthier women. Table 2 shows the multivariate incidence rate ratios (IRRs) for associations of various demographic, clinical, and laboratory indicators with incident pregnancy. Of note, accounting for other factors, incidence of pregnancy was much higher in younger than older women, with rate ratios of 13.2 (95% CL 8.4, 20.8) and 10.8 (95% CL 7.3, 16.1) comparing women ages 18–25 and 25–30 both to women ages 40–45.

In both crude and adjusted analysis, incidence of pregnancy was lower with lower CD4 count, especially among women with CD4 counts ≤100 cells/mm^3; surprisingly, there was no reduction in incidence rate of pregnancy associated with CD4 counts in the 101–200 cells/mm^3 range compared to higher CD4 counts. In an additional simplified model, we found only mild and inconsistent interaction between the effect of age and CD4 count (dichotomized at 100 cells/mm^3); what effect there was showed a slightly reduced impact of age on incidence of pregnancy among women with CD4 counts ≤100 cells/mm^3.

Incidence of pregnancy differed somewhat by drug regimen, with higher crude rates of pregnancy among women receiving lopinavir-ritonavir and nevirapine; however, in

Table 2: Incident rate and adjusted incident rate ratio for association of demographic, clinical, and laboratory indicators with incident pregnancy among antiretroviral therapy-naïve 18–45-year-old women initiating HAART in Johannesburg.

Demographics	Incidence rate, crude, per 100 person-years	Rate ratio, adjusted (95% confidence limits)
Current age (years)		
18–24.9	10.4 (8.2, 13.2)	13.21 (8.41, 20.75)
25–29.9	9.1 (8.0, 10.4)	10.81 (7.26, 16.09)
30–34.9	7.0 (6.2, 7.8)	7.93 (5.37, 11.70)
35–39.9	3.6 (3.0, 4.2)	4.01 (2.69, 5.99)
40–45.0	0.9 (0.6, 1.3)	1
Baseline pregnancy		
Pregnant	6.2 (5.1, 7.7)	0.80 (0.63, 1.03)
Not pregnant	5.0 (4.7, 5.5)	1
Clinical (all time-updated)		
HAART regimen		
Includes EFV	4.7 (4.3, 5.2)	1
Includes LPVr	5.6 (4.7, 6.7)	1.01 (0.82, 1.26)
Includes NVP	8.2 (6.7, 9.9)	1.19 (0.94, 1.50)
Body mass index (kg/m^2)		
<18.5	3.7 (2.6, 5.2)	1
18.5–24.9	5.2 (4.7, 5.8)	1.04 (0.71, 1.53)
25.0–29.9	5.5 (4.8, 6.2)	1.16 (0.78, 1.72)
≥30	5.2 (4.3, 6.2)	1.19 (0.79, 1.80)
Laboratory (all time updated)		
Hemoglobin‡		
Normal	5.3 (4.9, 5.8)	1
Low	4.5 (3.7, 5.3)	0.96 (0.76, 1.20)
CD4 count (cells/mm^3)		
≤50	2.1 (1.3, 3.3)	0.33 (0.15, 0.75)
51–100	3.2 (2.2, 4.7)	0.68 (0.42, 1.10)
101–200	5.4 (4.5, 6.3)	0.96 (0.77, 1.20)
201–350	5.5 (4.8, 6.3)	
351–500	6.1 (5.3, 7.1)	1
>500	5.0 (4.2, 5.9)	
Viral load (copies/mL)		
≤400	5.5 (5.0, 5.9)	1
401–10,000	5.1 (3.6, 7.3)	0.86 (0.59, 1.25)
>10,000	4.0 (2.8, 5.7)	0.88 (0.60, 1.29)
Adherence		
0–79%	3.7 (2.7, 5.3)	0.67 (0.45, 1.01)
80%–94%	5.9 (5.2, 6.8)	1.13 (0.95, 1.34)
≥95%	5.0 (4.5, 5.5)	1

‡After adjustment for altitude, lower limit of normal hemoglobin is 11.35 g/dL for non-pregnant women.

a multivariate predictive model controlling for other predictors of pregnancy these differences were not significant. Having a measured adherence under 80% was associated with lower incidence of pregnancy, with IRR = 0.67 (95% CL 0.45, 1.01) compared to adherence ≥95%.

In addition to the time-updated predictors of pregnancy noted above, we also examined baseline predictors of incident pregnancy, especially age and CD4 count. Figures 2(a) and 2(b) show cumulative incidence of first pregnancy by *baseline* age category, stratified by *baseline* CD4 count dichotomized at 100 cells/mm^3, among women alive and in care. Of note, cumulative incidence of pregnancy is extremely high among all women who initiated HAART between the ages of 18 and 25 regardless of baseline CD4 count.

3.5. Sensitivity Analyses for Predictors of Incident Pregnancy. We performed three sensitivity analyses of these data. First, we fit a discrete time proportional hazards model, Cox proportional hazards model, for these same data, finding

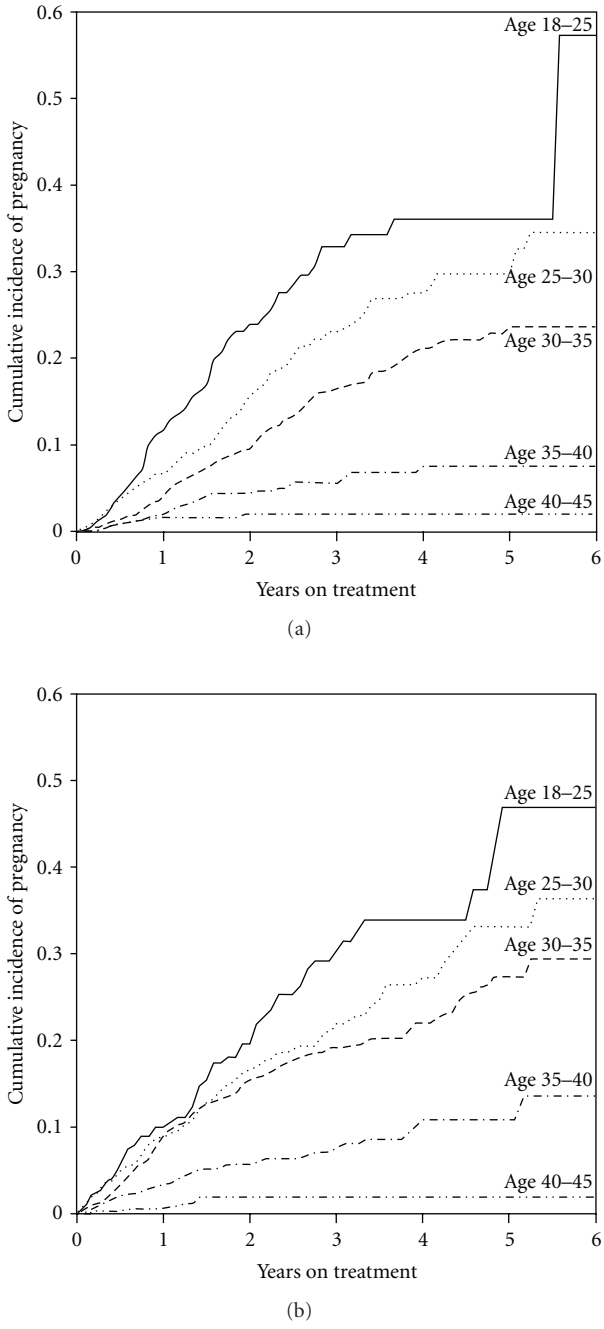

Figure 2: Cumulative incidence of first pregnancy among 5,996 women initiating HAART in Johannesburg, South Africa, from time of HAART initiation, by baseline age and baseline CD4 count: (a) $\leq$100 cells/mm^3; (b) >100 cells/mm^3. Curves are estimated using the extended Kaplan-Meier method.

similar findings to those reported. We looked at results separately by baseline pregnancy status; in this case, rate ratios for incidence of pregnancy among nonpregnant women were similar to overall rate ratios (Table 2); we had insufficient numbers to fit the multivariate model among baseline pregnant women alone or to fit a model including interactions for all variables with prevalent pregnancy status.

Finally, there were substantial missing data in the main analysis: a total of 23,425 of 169,138 person-months, or about 14% of observations. However, 85% ($n = 20,020$) of these missing observations were due to missing viral load data, so we reran the multivariate regression model leaving out viral load measurements—so in this analysis, 98% of the 169,138 possible observations were used. In this last sensitivity analysis, the key differences from Table 2 were (a) a slight rise in rate ratio associated with high body mass index (point estimates moved from 1.04–1.19 in Table 2 to 1.25–1.44, though none reached statistical significance at a P-value of 0.05) and (b) a significant effect of nevirapine on incidence of pregnancy (IRR 1.31, 95% CL 1.06, 1.62).

3.6. Efavirenz Exposure. First-trimester exposure to efavirenz is believed to be associated with an increased risk of congenital abnormalities [14, 15], although one systematic review disagrees [16]. In these data, 522 (72%) of pregnancies were exposed to efavirenz. In separate work, several clinical investigators from the TLC followed up infants exposed to efavirenz *in utero*, investigating 136 and analyzing 41 for congenital abnormalities and for developmental delays with the Denver Developmental Screening Test. No congenital abnormalities were identified. We found 30 infants to be within normal limits, and 11 infants to be suspect for neurodevelopment delay. This work was presented in conference [17] and included in the systematic review noted above [16].

4. Discussion and Conclusion

Planning for the integration of fertility or prenatal care services with clinical HIV services requires a clear understanding of which women will become pregnant and at what rates. In this observational study of HIV-positive women in urban South Africa, we found that pregnancy was relatively common after HAART initiation, reaching an estimated cumulative incidence of 52% among women who were 18–25 when they initiated HAART.

A recent study by Myer et al. reported on the incidence of 589 pregnancies after initiation of HAART among 4,531 women in seven African countries [6]. However, the generalizability of these findings may be somewhat limited by the fact that all these women entered care through prevention of mother-to-child transmission of HIV programs; by virtue of pregnancy, they may have been healthier than women who initiated HAART because they were sick [18] and—for this reason and others—may have been more likely to experience subsequent pregnancy. In addition, the main results reported by Myer et al. were a mix of very high and low pregnancy-incidence settings, with by-country rates ranging from 21.7 per 100 person-years in Rwanda to 3.3 (95% CL 2.6, 4.2) per 100 person-years in three urban sites in South Africa, from both pre- and post-HAART initiation. Our results show an overall higher rate of 5.2 per 100 person-years in only women who have initiated HAART. Our work shows similar incidence rates by age category: Myer et al. reported a rate of 11.5 (95% CL 9.4, 14.0) per 100 person-years among women under age 25 and on antiretroviral therapy; we reported a

rate of 10.4 (8.2, 13.3) per 100 person-years. The relatively high rates of pregnancy seen here, taken in context with recent results suggesting that pregnancy during HAART is associated with increased rates of virologic failure [11, 19], point to the need to better integrate reproductive healthcare services with provision of antiretroviral therapy.

Previous work [11] and theory [20] both suggest that women who are pregnant at baseline may respond to HAART in substantially different ways compared with nonpregnant women, in part because their initiation onto HAART may have more to do with their pregnancy status rather than their immune status. Here, we had insufficient data to evaluate whether predictors of incident pregnancy differ substantially by baseline pregnancy status. We saw a higher crude rate of incident pregnancy in women who were pregnant at baseline (6.2 versus 5.0 pregnancies per 100 person-years), but a slight reduction in relative rate (IRR 0.80, 95% CL 0.62, 1.03) in multivariate analysis. The lowered relative rate in multivariate analysis may be the result of a desire to space out births and/or a period of lowered risk of new pregnancy immediately postpartum (e.g., due to lactational amenorrhea). However, prevalent pregnant women are about twice as likely to be lost to followup as non-prevalent pregnant women; this finding should, therefore, not be overinterpreted.

There are several limitations of this work. Chief among these is our lack of data on use of contraception. However, it is likely that contraceptive use in this setting is likely to be lower than in the South African sites evaluated by Myer et al., as that work examined women who were accessing prevention of mother-to-child transmission services [6]. The present work deals with a general adult population, in which access to contraceptives may be more typical of the experience of an average South African woman presenting for general HIV care [21]; further, contraceptives are not offered at the pharmacy where TLC patients receive their antiretroviral medications, which is likely to further depress usage. Future studies will assess the impact and efficacy of contraception in this setting as well as assess unmet needs for contraception in the adult female population of this clinic. In addition, we analyzed observational data from a clinical database, and thus misclassification of exposure (particularly, start and end dates of pregnancies), outcome, and other factors cannot be ruled out. However, our sensitivity analyses support the results of our main analysis, and as noted above the TLC database has been previously validated for accuracy [12].

A final, and critical, limitation is that, while it is tempting to interpret the adjusted rate ratios reported in Table 2 as statements of causality (e.g., if we were to intervene on factor X, the rate of pregnancy would change by Y), such causal statements are not justifiable without substantial further assumptions and caveats [22]. Without further study, the numbers reported in Table 2 should be considered associations and predictions, not statements of causality.

In this large study of nearly 6,000 antiretroviral therapy-naïve women initiating HAART in Johannesburg, we found a high rate of pregnancy, especially among younger women. With very high numbers of HIV-infected young women in South Africa [5], incident pregnancy among women receiving HAART is an important issue with implications both for maternal response to HAART [11] as well as potentially for mother-to-child-transmission of HIV. It will be critical in coming years both to integrate contraceptive counseling and/or antenatal care into settings where HAART is provided [23] as well as to ensure that women who get reproductive or antenatal care in other facilities are able to transition between care centers smoothly and without becoming lost to care. In addition, such a high rate of pregnancy makes it critical that we better understand the impact and timing of pregnancy after HAART initiation on outcomes of HAART, as well as of pregnancy in both mother and child.

Authors' Contribution

D. Westreich cleaned the data, performed statistical analysis, and wrote the first draft of the paper as well as edited subsequent drafts. M. Maskew collected data, helped manage the database, helped clean the database, and helped write and edit the paper. D. Rubel, P. MmacDonald, P. Majuba, and I. Jaffray collected data, performed clinical investigation of efavirenz-exposed infants, and reviewed drafts of the paper. All authors have approved the final version of the paper.

Ethical Approval

This analysis of de-identified research was declared exempt from review by both the University of the Witwatersrand (Protocol M060626, 30 June 2006) and Duke University (Protocol Pro00025267, 13 October 2010). The clinical followup of efavirenz-exposed infants was approved by the University of the Witwatersrand (Protocol M070706, 16 August 2007).

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Conflict of Interests

The authors declared that they have relevant interests to disclose.

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