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Tenofovir use and pregnancy among women initiating HAART

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Abstract

Objective—Recent studies have raised concerns about a change in rates of pregnancy among HIV-negative women exposed to tenofovir. Here, our objective was to determine among HIV-positive women whether use of tenofovir at HAART initiation or thereafter is associated with subsequent changes in incidence of pregnancy.

Design—Analysis of prospectively collected clinical data.

Methods—We used Cox proportional hazards models and logistic regression to estimate hazard ratios and odds-ratios for the association of baseline tenofovir use and time to first incident pregnancy. We used marginal structural Cox models to estimate hazard ratios for the association of current tenofovir use and time to first incident pregnancy.

Results—We studied 7,275 women, of whom 1,199 were initiated on tenofovir-based HAART regimens, and who experienced a total of 894 pregnancies in 17,200 person-years of follow-up. Analyses showed slight reductions in hazards of pregnancy among women who used tenofovir, but without sufficient precision to draw strong conclusions. Sensitivity analyses confirmed main results.

Conclusions—Tenofovir may be associated with a lower hazard or rate of pregnancy in women receiving HAART. However, conclusions are limited by low precision, the observational nature of the data, and possible uncontrolled confounding by temporal trends in contraception use and other factors.

INTRODUCTION

Women of child-bearing age in South Africa have more than three times the estimated prevalence of HIV infection compared with young men. Among pregnant women, HIV prevalence has been estimated as high as 40% in some age groups and areas [1, 2]; in addition, pregnancy is common after the initiation of HAART for a woman's health throughout sub-Saharan Africa [3].

The issue of whether tenofovir exposure has any impact on pregnancy rate is increasingly of interest. Evidence from the recent FEM-PrEP study of pre-exposure prophylaxis for HIV-

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negative women suggests that there may be an increased risk of becoming pregnant for women using tenofovir-based PrEP [4]. In contrast, work from the CAPRISA 004 microbicide trial showed a slightly lower rate of pregnancy among women using tenofovir gel compared to those using placebo, although these results were not statistically significant [5]; while this may be due to increased risks of oral contraceptive failure, such an effect would be “unexpected and inconsistent with known drug interactions involving tenofovir and contraceptive hormones”[6].

It is unknown at present what impact, if any, oral tenofovir might have on rates of pregnancy. Since 1 April 2010, it has been standard practice in South Africa to initiate women on HAART regimens containing tenofovir, rather than stavudine-containing regimens. Here we sought to explore the overall association of tenofovir-based therapy and incident pregnancy in a large population of HIV-positive women initiating HAART in South Africa.

METHODS

The study was conducted using previously collected clinical data from the Themba Lethu Clinic, a cohort of adults initiating highly active antiretroviral therapy in Johannesburg, South Africa. The Clinic is sited at the regional Helen Joseph Hospital in urban Johannesburg, and has over 17,000 patients in care and is the largest single clinic providing HAART in South Africa, and one of the largest HAART clinics worldwide.

We evaluated all HAART-naïve, non-pregnant women between the ages of 18 and 45 initiating HAART between 1 April 2004 and 31 March 2011 at the Clinic. These women were followed until the earliest of 1) 30 September 2011, 2) drop-out, 3) transfer to another care facility, or 4) death. Women were included if they started one of the following standard treatment regimens: EITHER stavudine or tenofovir, PLUS lamivudine, PLUS EITHER efavirenz, nevirapine, or lopinavir-ritonavir (Kaletra). Further details of the clinic population, clinical and research procedures can be found in [7].

To estimate the effect of baseline use of tenofovir versus baseline use of stavudine on time to first incident pregnancy, we used adjusted Cox proportional hazards models and log-binomial models to estimate hazard ratios and risk ratios. We adjusted for confounders listed in Table 1, using five-knot cubic splines [8] (with knots at the 5th, 25th, 50th, 75th, and 95th percentiles) to adjust for critical continuous covariates (age; CD4 count; body mass index). To estimate the effect of *current* use of tenofovir versus *current* use of other drug regimens (largely stavudine) on time to first incident pregnancy, we used inverse probability of treatment weighted marginal structural Cox proportional hazards models [9], controlling for the same covariates as well as time-updated covariates of weight, body mass index, hemoglobin, CD4 count, CD4 percentage, and adherence to HAART. In this analysis, we treated initiation of tenofovir in an intent-to-treat, once-treated always-treated manner, which correctly classified 95.6% of person-time.

In all analyses, the primary analysis was limited to the first 12 months after HAART initiation, with more follow-up time included in sensitivity analyses. Since HAART regimen was so strongly influenced by time period due to changes in the national treatment guidelines, we did not control for date of initiation of HAART in main analysis; in sensitivity analysis, we restricted to later periods (after 30 September 2007, and after 30 September 2008) when controlling for date of initiation to ensure positivity by this variable [10]. In addition, because there was generally less follow-up time for tenofovir-based regimens, we performed some analyses which limited follow-up time to 12 months after initiation of HAART.

RESULTS

A total of 7534 women were considered, of whom 7275 were on one of the six regimens specified (Table 1). Of these, 6076 (84%) were on stavudine-based regimen, while the remaining 1199 (16%) were on tenofovir-based regimens. In general, women initiating tenofovir-based regimens were healthier, with median CD4 count 129 (interquartile range [IQR] 56, 193) cells/mm³ compared with median (IQR) CD4 of 90 (34, 159) cells/mm³ among women initiating stavudine-based regimen, and similarly had less very low body mass index (<8.5 kg/m²) and less active tuberculosis (Table 1). Interestingly, while the proportion of women on tenofovir with low hemoglobin (<1.35 g/dL) was lower than those on stavudine, women on tenofovir had *more* very low hemoglobin (< g/dL).

Over a total follow-up time of approximately 17,200 person-years, women experienced a total of 894 first incident pregnancies: 57 among 1199 tenofovir-exposed women (4.8%), and 837 among the 6076 stavudine-exposed women (13.8%). Overall median time from initiation of HAART to first pregnancy was 14 months (IQR 7, 26). Because follow-up time differed between tenofovir-exposed and unexposed women, median time to pregnancy differed substantially between the two groups (15 months in stavudine-exposed women, 6 months in tenofovir-exposed women). The overall rate of pregnancy among tenofovir-exposed women was 4.9/100 person-years, and in stavudine-exposed women was 5.2/100 person-years, for a crude rate ratio of 0.95 (95% confidence limits [CL] 0.72, 1.24).

When considering women *initiated* on tenofovir compared to those initiated on stavudine, crude Kaplan-Meier curves suggested a reduced incidence of pregnancy for women on tenofovir compared to those initiated on stavudine (Figure 1), both in the first 12 months of follow-up and overall. A crude Cox proportional hazards model for the first 12 months for the effect of baseline tenofovir exposure compared to baseline stavudine exposure on incident pregnancy gave similar results, hazard ratio (HR)=0.71 (95% CL 0.52, 0.97). Adjusted Cox regression for the first 12 months was similar, but closer to the null and less precise, HR=0.78 (95% CL 0.55, 1.11). An adjusted logistic regression for risk by 12 months also gave similar results (OR=0.67, 95% CL 0.47, 0.98). Restricting to individuals initiating HAART after 30 September 2007 (and adjusting for calendar date) gave an estimate similar to main analysis (HR=0.72, 95% CL 0.43, 1.19); restricting to initiation after 30 September 2008 gave an estimate somewhat closer to the null (HR=0.82, 95% CL 0.45, 1.50).

When using *current* regimen instead of baseline regimen over the first 12 months of follow-up, we found a crude HR=0.72 (95% CL 0.53, 0.97). Using the marginal structural (weighted) Cox model to properly adjust for confounding of time-varying initiation of tenofovir use, weights were well behaved (mean of weights after truncation at 0.1st and 99.9th percentiles, 1.000); weighted HR was 0.80 (0.56, 1.14). When restricting to those initiating HAART after 30 September 2007 or 2008, weighted results remained similar.

Over the entire follow-up period for the effect of baseline tenofovir exposure, the crude Cox model gave an estimate of HR=0.75 (95% CL 0.57, 0.99) and the adjusted Cox models an estimate of HR=0.89 (95% CL 0.66, 1.21). Over the entire follow-up period for the effect of current tenofovir exposure, the crude Cox model gave an estimate of HR=0.84 (95% CL 0.69, 1.03) and the marginal structural (weighted) Cox model which adjusted for confounding of time-varying use of tenofovir gave an estimate of HR=0.79 (95% CL 0.62, 1.00).

DISCUSSION

Since the World Health Organisation revised its guidelines for antiretroviral therapy in 2010 to no longer recommend the use of stavudine as first-line antiretroviral therapy [11], drugs like tenofovir have become more widely used in resource-limited settings. Providing evidence to address questions around the effects and drug interactions of tenofovir is thus gaining clinical, operational, and public health significance. Here, we investigated the related question of whether oral tenofovir influences pregnancy rates among HIV-positive women initiating HAART for their own health in an urban South African setting. We found a suggestion of a decreased incidence of pregnancy in the first 12 months of HAART, as well as thereafter, associated with use of tenofovir compared to use of stavudine, a finding supported in a wide range of analyses. However, results were generally imprecise, so no strong conclusions can be drawn from these results.

The recent finding of an increased rate of incident pregnancy among women using tenofovir-based PrEP enrolled in the FEM-PrEP trial [4] and a decreased rate in tenofovir-exposed women in CAPRISA 002 [5] points to the possibility that tenofovir impacts rates of pregnancy. However, our results are clearly not directly comparable to those reported in FEM-PrEP or CAPRISA 004; this work studies an HIV-positive population receiving HAART, while the microbicide studies were conducted among HIV-negative women using tenofovir or other drugs to prevent infection.

This work had several limitations, among them our inability to control for several potential confounders, including time since HIV diagnosis and marital status. The major limitation of this work was the non-overlapping calendar years of exposure, which may point to uncontrolled confounding. For example, use of contraception was not controlled for in this analysis; if trends in use of and adherence to contraception in this group of women changed over time, these results might be explained by increased use of contraception in later years.

However, this point also raises the key strength of this analysis: that our exposure (tenofovir use and stavudine use) is driven largely by calendar year rather than potentially confounding factors, making some of these analyses analogous to instrumental variable analysis: in particular, the baseline-tenofovir exposure analysis. While contraceptive coverage and adherence (for example) may have changed over time, any such changes were unrelated to changes in policy which led to women being initiated on tenofovir in later time periods. Except in the presence of strong temporal trends, then, we expect the amount of residual confounding in this analysis to be relatively small. The sensitivity analysis limiting time period to the period after 30 September 2008 broadly supports this argument.

These results suggest that women receiving tenofovir may have slightly lower incidence of pregnancy compared with women receiving stavudine for treatment of HIV. More research is needed to confirm this initial finding, and – if necessary – to elucidate etiologic mechanisms.

REFERENCES

1. Pettifor AE, Rees HV, Kleinschmidt I, Steffenson AE, MacPhail C, Hlongwa-Madikizela L, et al. Young people's sexual health in South Africa: HIV prevalence and sexual behaviors from a nationally representative household survey. *AIDS*. 2005; 19:1525–1534. [PubMed: 16135907]
2. UNAIDS/WHO. *AIDS Epidemic Update 2007*. Geneva: 2007. <http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2007default.asp>
3. 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. [PubMed: 20161723]

4. FHI360. FEM-PrEP Project. Research Triangle Park, NC: 2011. <http://www.fhi360.org/en/Research/Projects/FEM-PrEP.htm> [Accessed 24 February 2012]
5. Sibeko S, Baxter C, Yende N, Karim QA, Karim SS. Contraceptive choices, pregnancy rates, and outcomes in a microbicide trial. *Obstet Gynecol.* 2011; 118:895–904. [PubMed: 21934454]
6. FHI360. Pregnancy and Contraceptive Effectiveness in the FEM-PrEP Trial. Research Triangle Park, NC: 2011. <http://www.fhi360.org/en/Research/Projects/FEM-PrEP.htm> [Accessed 24 February 2012]
7. Fox MP, Maskew M, Macphail AP, Long L, Brennan AT, Westreich D, et al. Cohort Profile: The Themba Lethu Clinical Cohort, Johannesburg, South Africa. *Int J Epidemiol.* 2012
8. Howe CJ, Cole SR, Westreich DJ, Greenland S, Napravnik S, Eron JJ. Splines for trend analysis and continuous confounder control. *Epidemiology.* 2011; 22:874–875. [PubMed: 21968779]
9. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology.* 2000; 11:550–560. [PubMed: 10955408]
10. Westreich D, Cole SR. Invited commentary: positivity in practice. *Am J Epidemiol.* 2010; 171:674–677. discussion 678–681. [PubMed: 20139125]
11. WHO. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Recommendations for a public health approach. Geneva: 2010. www.who.int/hiv/pub/mtct/antiretroviral2010/.

Regimen	Number at risk by month						
	0	6	12	18	24	30	36
Stavudine	6076	5462	4374	3874	3263	2753	2292
Tenofovir	1199	1113	526	92	40	29	21

Figure 1.
Cumulative incidence of first incident pregnancy among 7,275 women initiating HAART by baseline exposure to tenofovir or stavudine in the first three years of follow-up.

Table 1

Baseline characteristics of 7,275 women initiating HAART stratified by baseline exposure to tenofovir or stavudine. All numbers are given as N(%) except ‡ as median (interquartile range).

Characteristic	Tenofovir (TDF) <i>n</i> =1199	Stavudine (d4T) <i>n</i> =6076
Follow-up time, months	11 (7, 15)	26 (10, 49)
Demographic		
Age at initiation‡	34 (29, 39)	33 (29, 38)
History of smoking	91 (7.6)	319 (5.3)
Employed	630 (52.5)	2513 (41.4)
Completed secondary education	2350 (39.2)	399 (33.3)
Clinical		
Current treatment for tuberculosis	159 (13.3)	1040 (17.1)
WHO stage III or IV	380 (40.0)	2356 (43.3)
Body mass index <i>kg/m</i> ²		
<18.5	154 (14.1)	1057 (18.4)
18.5–24.9	560 (51.2)	3118 (54.1)
25.0–29.9	252 (23.1)	1078 (18.7)
≥30	127 (11.6)	507 (8.8)
Drug regimen includes:		
Efavirenz	1094 (91.2)	5355 (88.1)
Nevirapine	78 (6.5)	548 (9.0)
Lopinavir-ritonavir	27 (2.3)	173 (2.9)
Laboratory		
CD4 cell count category <i>cells/mm</i> ³		
≤50	241 (23.4)	1952 (33.4)
51–100	178 (17.3)	1212 (20.7)
101–200	391 (38.0)	2070 (35.4)
201–350	219 (21.3)	609 (10.4)
Hemoglobin ‡		
Low	562 (53.0)	3322 (56.6)
Very low	224 (18.7)	730 (12.0)

‡ Very low hemoglobin is defined as is defined as <8 g/dL. Low hemoglobin is defined as 8.00 – 11.35 g/dL, a definition which adjusts for the altitude of Johannesburg.