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The effect of pregnancy and the postpartum period on adherence to antiretroviral therapy among HIV-infected women established on treatment

Cassidy E. HENEGAR, PhD[1], **Daniel J. WESTREICH, PhD**[1], **Mhairi MASKEW, MBBCH**[2], **William C. MILLER, MD, PhD**[3], **M. Alan BROOKHART, PhD**[1], and **Annelies VAN RIE, MD, PhD**[1]

[1]Department of Epidemiology, The University of North Carolina at Chapel Hill, Chapel Hill, NC USA

[2]Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[3]Division of Infectious Diseases, Department of Medicine, School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract

Among women who become pregnant after initiating highly active antiretroviral therapy (HAART), few data describe the effect of pregnancy and postpartum on adherence. We conducted a retrospective clinical cohort study among therapy-naive women (ages 18–45) initiating HAART in Johannesburg, South Africa. Among 7,510 women in our analysis, 896 experienced a pregnancy after starting HAART. Compared to non-pregnant periods of follow-up, there was an increased risk of non-adherence during the postpartum period (weighted risk ratio (RR): 1.46, 95% confidence interval (CI): 1.17, 1.82), but not during pregnancy itself (weighted RR: 0.95, 95% CI: 0.78, 1.17).

Keywords

pregnancy; adherence; highly active antiretroviral therapy; South Africa

INTRODUCTION

In South Africa, women of child-bearing age are disproportionately affected by HIV. Prevalence of HIV among young women is as much as 3 times that among young men [1], and annual antenatal surveillance data for the country indicate that 30% of pregnant women

Correspondence: Cassidy Henegar, PhD, Department of Epidemiology, The University of North Carolina at Chapel Hill, CB 7435, Chapel Hill, NC 27599, Phone: 919-274-6952, cashene@email.unc.edu.

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between the ages of 15 and 49 are infected with HIV. [2] As a result of more widespread access to affordable antiretroviral therapy and the recommendation of earlier thresholds for treatment initiation, HIV-infected women in South Africa are living longer, healthier lives, and an increasing number are becoming pregnant while on ART. [3,4]

The use of highly active antiretroviral therapy (HAART) during pregnancy can dramatically decrease the risk of mother-to-child transmission of HIV, in addition to directly improving maternal health and survival. [5] In order for HAART to be fully effective in reducing HIV viral load, a high degree of adherence is required. [6, 7] Prior studies have suggested that pregnancy and the postpartum period may be associated with sub-optimal adherence. [8] Most of these reports, particularly those from low-resource settings, have focused on women initiating treatment with ART during pregnancy for the primary purpose of preventing vertical transmission of HIV. The effect of pregnancy on adherence may be different for the growing population of women who begin lifelong treatment with HAART for their own health, prior to becoming pregnant. Here we describe the risk of non-adherence during pregnancy and the postpartum period among women who initiated HAART for their own health at the Themba Lethu Clinic, an adult antiretroviral therapy clinical in Johannesburg, South Africa.

METHODS

Study population

We studied antiretroviral therapy-naïve women ages 18 to 45 who initiated HAART at Themba Lethu Clinic between 1 April 2004 and 31 March 2011. Women were followed until they died, transferred care to another facility or were lost to follow-up. Women who experienced none of these outcomes and who remained in treatment at the end of data collection were administratively censored at the end of follow-up (30 September 2011). Women initiating HAART during a pregnancy were excluded from this analysis as these women are typically healthier than women initiating HAART for their own health. [9]

Definitions

The primary exposures of interest for this analysis were (i) new pregnancy after HAART initiation (*incident pregnancy*) and (ii) the subsequent postpartum period, defined as six months after the end of pregnancy. The start and end dates of incident pregnancies were extracted from electronic patient medical records. Women who experienced a pregnancy during follow-up were censored at the end of the six month postpartum period. Thus, for each month of follow-up beginning at HAART initiation, a woman's exposure status was identified as 1) not-pregnant, 2) pregnant, or 3) postpartum. In our primary analysis, women who experienced incident pregnancy but were missing an end date for the pregnancy were excluded once they became pregnant.

The outcome of interest was non-adherence compared to adherence. Adherence was assessed at each pharmacy visit to refill antiretroviral prescriptions, which occurred either monthly or every other month. Non-adherence was defined as having pills for less than

100% of days between refills in the 60 days prior to the current pharmacy visit; the selection of this measure is described in other work. [10]

Statistical Analyses

Baseline characteristics for eligible women were reported with descriptive statistics including chi-square tests to compare categorical variables and t-tests to compare means. The following baseline variables were included as confounders in multivariate analyses: age, employment status, WHO stage, treatment for tuberculosis, inclusion of efavirenz (EFV) or stavudine (d4T) in the initial HAART regimen, and initial CD4 (T cell) count, hemoglobin and body mass index measurements. Baseline HIV viral load is not routinely collected in this setting.

We used marginal structural models to account for the possibility of time-varying confounders affected by prior exposure. [11] Our models included time-updated measurements for CD4 (T cell) count, HIV viral load, hemoglobin, body mass index, EFV and d4T in the most recent HAART regimen. Typical construction of inverse probability weights model a single transition between two exposure states; usually from unexposed to exposed. [12] Our analysis required a novel weighting structure incorporating the cumulative probability of exposure transitions between three states, specifically: not-pregnant to pregnant (a transition for which all women were eligible, but which was experienced by only some women) and pregnant to postpartum (for which only pregnant women were eligible, and which all pregnant women experienced). We used these weights to fit marginal structural log-binomial regression models to estimate relative risks of non-adherence during periods of pregnancy, postpartum, and non-pregnancy. Generalized estimating equations were used to account for repeated measures within individuals. Restricted cubic splines were used to flexibly and efficiently control for the continuous and time-updated variables of age, CD4 (T cell) count, HIV viral load, and time-on-study. [13]

Sensitivity Analyses

In order to estimate the potential impact of inaccuracies in self-reported pregnancy start and end dates, we performed analyses allowing adjustments to pregnancy dates, including shifting the pregnancy start date earlier by 3 months, the approximate equivalent of one trimester, and fixing all pregnancy start dates 9 months prior to reported end dates. Sensitivity analyses to account for missing pregnancy end dates included fixing length of pregnancy nine months from the reported start date, and using multiple imputation to fill in end dates. Additional sensitivity analyses included using an extended 12 month definition of the postpartum period, restricting analysis only to women experiencing pregnancy during follow-up, and examining the effect of pregnancy and postpartum adherence only among those women experiencing all three exposures.

RESULTS

A total of 7,510 previously treatment-naïve women initiating HAART at the clinic between April 1, 2004 and March 31, 2011 were eligible for inclusion in this analysis. A first incident pregnancy was experienced by 896 of these women. In general, pregnancy after starting

HAART was more common among women that were younger and healthier at the time of treatment initiation. Median follow-up time for all women was 27 months (interquartile range [IQR] 11, 52), while median time from HAART initiation to first incident pregnancy was 19 months (IQR 9,33).

Overall, women possessed pills for every day between pharmacy visits 89.1% of the time. Adherence based on our binary indicator was nearly identical when assessed in women who were not pregnant and pregnant at the time of a prescription refill, with 89.2% and 89.5% of pharmacy pickups during these periods, respectively, occurring before an individual ran out of pills. During the postpartum period, percentage of period during which women ran out of pills was slightly lower at 84.8%.

Our primary analysis compared the risk of being non-adherent during pregnancy or during the postpartum period with the risk of being non-adherent in the non-pregnant, non-postpartum person-time. In primary analysis, weighted models showed no change in risk between non-pregnant and pregnant women (weighted risk ratio [RR]: 0.95, 95% confidence interval [CI]: 0.78, 1.17), but an increased risk of non-adherence during the six month postpartum period following the end of a pregnancy (weighted RR: 1.46, 95% CI: 1.17, 1.82). (Table 1) Crude models showed similar results to weighted models (Table 1).

Results of our sensitivity analyses suggest that despite definitions used to classify pregnancy and postpartum exposed follow-up time, the estimated RRs for non-adherence are relatively durable. Extension of the pregnancy period 3 months prior to the reported start date (postpartum vs. not-pregnant, RR: 1.47, 95% CI: 1.20, 1.80), as well as adjustments to create a fixed 9 month pregnancy from reported end date (postpartum vs. not-pregnant, RR: 1.39: 95% CI 1.17, 1.65), showed a qualitatively similar relationship between postpartum exposure and adherence as the crude and primary weighted models.

A similar but less marked (as well as less precise) association was observed when the analysis was restricted to only women experiencing pregnancy (and comparing within women), with the pre-pregnancy period as the referent exposure (pregnancy RR: 1.06, 95% CI: 0.63, 1.77; postpartum RR: 1.32, 95% CI: 0.88, 1.98). The exclusion of early adherence assessments from restricting to follow-up six months or later after HAART initiation also had little effect on the point estimates.

Analyses to account for the common issue of missing pregnancy end dates (40.7%, n=365), including multiple imputation and fixed pregnancy end dates, indicated a smaller but still significant increased risk in the postpartum.

DISCUSSION

In a cohort of women beginning lifelong HAART for their own health, incident pregnancy after treatment initiation was associated with increased risk of non-adherence as measured by inadequate pill counts during the postpartum, but not pregnant, period. Using pharmacy-based measures, women demonstrated similar adherence to non-pregnant women during pregnancy itself.

There are several other published reports of suboptimal adherence to ART in the postpartum period. [8, 14, 15] The drop-off in adherence seen after pregnancy has been attributed to lifestyle changes and stressors associated with having a newborn, as well as shifting motivation for treatment. [16–18] Postpartum depression may also play a role in changes in maternal behavior. [19] In contrast, a desire to prevent mother-to-child transmission has been cited as a major driver of maternal adherence during pregnancy. [20]

Overall, the proportion of both pregnant and postpartum women with adequate adherence was higher than what has been seen in other settings, with 89% of refills for non-pregnant and pregnant women, and 85% of refills for postpartum women occurring on time. Pooled estimates for the proportion of adequate adherence reported in a recent meta-analysis were 76% during pregnancy and 53% during the postpartum period. [8] When restricted to treatment with combination ART, the estimate (combined for pregnant and postpartum) was even lower (63%). We also observed no decrease in adherence among pregnant women when compared to non-pregnancy or pre-pregnancy adherence measures. Few other studies have compared pregnant and non-pregnant women, with most indicating lower adherence during pregnancy. [21,22]

The high degree of adherence observed in our cohort may be partially attributable to the fact that we included only women who had initiated HAART for their own health while not pregnant. To our knowledge, this is the first study of pregnancy-related ART adherence restricted to this population: prior studies [8] have looked either exclusively at women starting antiretroviral therapy during pregnancy or a combination of women starting before and during pregnancy. Many women initiating HAART during pregnancy have (in addition) just been diagnosed with HIV through routine antenatal screening. The combination of starting a complex treatment regimen, as well as dealing with the implications of both a new HIV diagnosis and pregnancy, may lead to suboptimal adherence for these women.

Our study has the benefit of a large cohort and high quality data. Our findings are therefore likely generalizable to similar resource limited settings where pregnancy after HAART initiation is increasingly common. There are also limitations of this study, including potential reporting errors and missing data for pregnancy begin and end dates due to self-reported pregnancy status. Inaccurate reporting of pregnancy dates leads to misclassifying when women experienced pregnancy and the postpartum during their follow-up, which could potentially bias estimates of the effect of pregnancy and the postpartum on adherence. We conducted several sensitivity analyses to account for potential misclassification, however, and found that estimates were durable across analyses, suggesting limited impact of such misclassification.

With more HIV-infected women of reproductive age accessing and achieving viral load suppression on HAART, particularly in middle- and low-income countries, the incidence of pregnancy among women established on treatment is increasing. Although reported adherence was higher in this study than in some other settings, we still observed a need for targeted interventions in the postpartum period, in order to minimize risk of mother-to-child HIV transmission and ensure continued protection of maternal health. Further research is

needed among women established on HAART prior to pregnancy to identify risk factors for non-adherence specific to this population.

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Table 1

Association of incident pregnancy with adherence from main and sensitivity analyses. Models use “Pre-pregnancy/never pregnant” as the reference group.

Main analyses	RR	95% CI
Crude		
Pre-pregnancy/never-pregnant	1.	
Pregnancy	0.94	0.80, 1.10
Postpartum	1.40	1.19, 1.65
Weighted		
Pre-pregnancy/never-pregnant	1.	
Pregnancy	0.95	0.78, 1.17
Postpartum	1.46	1.17, 1.82
Sensitivity Analyses (weighted models)		
Pre-pregnant/never-pregnant (global referent)	1.	
Only among women experiencing pregnancy ±		
Pregnancy	1.06	0.63, 1.77
Postpartum	1.32	0.88, 1.98
Established on HAART+ *		
Pregnancy	0.96	0.78,1.19
Postpartum	1.49	1.20, 1.85
Start of pregnancy 9 months from end date		
Pregnancy	0.97	0.86, 1.12
Postpartum	1.39	1.17, 1.65
Fixed pregnancy length (9 months)		
Pregnancy	1.00	0.87, 1.17
Postpartum	1.23	1.01, 1.49
Start of pregnancy 3 months earlier		
Pregnancy	0.90	0.75,1.09
Postpartum	1.47	1.20, 1.80
Postpartum period of 12 months		
Pregnancy	1.08	0.80, 1.48
Postpartum	1.49	1.18, 2.09
Multiple imputation analysis		
Pregnancy	0.97	0.81, 1.13
Postpartum	1.34	1.11, 1.57

RR: risk ratio; 95% CI: 95% confidence interval

± referent group is pre-pregnancy person-time among those that became pregnant during follow-up

+ HAART: highly active antiretroviral therapy

* analysis among alive and in care at 6 months post-HAART initiation