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Live birth patterns among HIV-infected women before and after the availability of HAART

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Abstract

Objective— To investigate the relationship between HIV infection and childbearing before and after the availability of HAART.

Study Design— Enrollment in the Women's Interagency HIV Study took place in 1994–1995 (pre-HAART era), and again in 2001–2002 (HAART era). Live birth rates prior to enrollment were compared between treatment era cohorts for HIV-infected and HIV-uninfected women aged 15–44 years using Poisson regression. For HIV-infected women we included live births between HIV diagnosis date and study entry; the HAART era cohort included only women diagnosed with HIV in 1996 and after.

Results— Among HIV-infected women, the HAART era live birth rate was 150% higher than in the pre-HAART era ($p=.001$), vs. a 5% increase among HIV-uninfected women. The rate of increase in live birth rate was higher for women ≥ 35 years (vs. <25 , $p=.02$), and with $>$ high school education (vs. $<$ high school, $p=.05$.)

Conclusions— The availability of effective therapeutic interventions has profoundly impacted childbearing among HIV-infected women.

Keywords

HIV; women; reproductive decision-making; birth rate; highly active antiretroviral therapy

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Condensation

Live birth rates for HIV-infected women have dramatically increased since the widespread availability of HAART, reflecting its profound impact on reproductive decision-making in HIV-infected women.

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Introduction

The number of women living with HIV infection and AIDS has been increasing steadily worldwide, and women now account for approximately 50% of the 40 million adults living with HIV/AIDS globally¹. In the United States during 2001–2004, an estimated 45,146 women had HIV/AIDS diagnosed in the 33 states reporting to the Centers for Disease Control and Prevention, 75% of whom were aged 13–44 years². Since the majority of HIV-infected women are in the years of highest fertility, it is important to understand the interplay between their reproductive activities and HIV serostatus, and the factors that influence childbearing decisions.

Since 1996, highly active antiretroviral therapy (HAART) has been available in the United States, and has been shown to dramatically improve survival for individuals with HIV³, and to markedly reduce the rate of mother-to-child transmission of HIV^{4–6}. However, it is unclear whether these advantages have affected women's childbearing plans. Studies conducted prior to the widespread availability of HAART have revealed that HIV infection per se had not been a barrier to pregnancy^{7–9} though often the pregnancies occurred coincident with the diagnosis of HIV infection. In this report, we capitalize on a large cohort study of HIV-infected and at-risk women that recruited women of similar ages, backgrounds, and ethnicities in two waves: one before and one after HAART became available, in order to compare the influence of HIV-infection on childbearing in two eras bracketed by the availability of effective therapeutic interventions.

Materials and Methods

The Women's Interagency HIV Study (WIHS) is an ongoing prospective study of the natural history of HIV infection in women; 2,056 HIV seroprevalent and 569 seronegative participants were enrolled at six clinical consortia (Bronx, NY; Brooklyn, NY; Chicago, IL; San Francisco, CA; Los Angeles, CA; and Washington D.C.) between October 1994 and November 1995. A second wave of recruitment at the same sites took place between October 2001 and November 2002 enrolling an additional 738 seropositive (254 HAART-naïve; 484 HAART-experienced) and 406 seronegative women.

The recruitment methods and data collection procedures of the WIHS have been previously described¹⁰. Briefly, participants undergo semiannual visits that include an interviewer-administered questionnaire, a physical examination, and the collection of blood and gynecologic specimens. Marital status, education level, annual income, and HIV-exposure category were determined from self-report at baseline. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D), with those scoring ≥ 16 classified as depressed¹¹.

At their baseline visit, all participants were asked when they first learned of their HIV serostatus. This analysis focuses on live birth rates between the first HIV-positive test and study entry. For seronegative controls we included live births that occurred between the ages of 15 and 44 years, prior to study enrollment. Women were considered to be at risk for pregnancy if they were of reproductive age (15–44 years) and had not undergone a hysterectomy or sterilization.

Periods corresponding to treatment era were used to examine population effects of HAART availability on HIV-infected women. Thus we were assessing whether being HIV infected at a time when HAART was available, whether or not individual women used it, influenced reproductive decision-making. The initial recruitment phase was defined as the pre-HAART era cohort, and the second recruitment phase was defined as HAART era cohort, as HAART was widely available during this time frame. Live birth rates were the number of reported live

births per 1000 person-years, and were compared between the pre-HAART and HAART era cohorts.

For HIV-infected women in the HAART era cohort, only those who tested HIV-positive in 1996 or later were included. Person years of exposure for the HIV-infected women included the number of years between the date of the first positive HIV test and the date of study enrollment. Person years of exposure for the HIV-uninfected women included the number of years between age 15 and the age at study enrollment or up to age 44.

Statistical Analysis

We compared differences in the live birth rates between the pre-HAART and HAART era cohorts for HIV-infected and uninfected women using Poisson regression models, using log person-years to represent follow-up time. The models were scaled using the Pearson Q statistic divided by its degrees of freedom¹². Interactions between cohort (pre-HAART vs. HAART era), and HIV serostatus were examined after adjusting for follow-up time and selected covariates, such as age, race/ethnicity, education, HIV exposure risk category, and depressive symptoms. Reported p values (shown in Table 2) refer to the level of statistical significance for these interactions. Changes in live birth rate between the cohorts by HIV serostatus were assessed for statistical significance. Goodness of fit measures were obtained and were adequate for each model examined. Analyses were conducted using SAS version 9.1 software (SAS Institute, Cary, NC.)

Results

Baseline characteristics for WIHS participants in the pre-HAART (1994–5) and HAART era (2001–2) cohorts are shown in Table I. The majority of women in both cohorts were of racial or ethnic minority background, and reported an annual income of less than \$12,000. WIHS participants recruited in the HAART era were slightly younger (median age 33 yrs for HIV+, and 29 yrs for HIV– women in the HAART era cohort vs. 36 yrs for HIV+, and 34 yrs for HIV– women in the pre-HAART cohort). They also had higher baseline CD4+ counts, with 9.2% of HIV-infected women having CD4+ counts below 200 cells/mm³ in the HAART era cohort vs. 29% in the pre-HAART cohort.

Of 2056 HIV seroprevalent women enrolled in the pre-HAART cohort, 2012 (97.9%) were at risk for pregnancy, and contributed 7573 person-years of data. All 569 seronegative women enrolled in the pre-HAART cohort were at-risk for pregnancy and contributed 10,673 person-years of data. An additional 738 HIV seroprevalent women were enrolled in 2001–2 as part of the HAART era cohort, and of these, 476 were at-risk for pregnancy in 1996 and after, and contributed 1,326 person-years of data. Of the additional 406 seronegative women enrolled in the HAART era cohort, all but one were at-risk for pregnancy, contributing 5,930 person-years of data.

For both the HIV-infected and uninfected women, the live birth rates in the HAART-era were higher than those during the pre-HAART era; however this difference was much more pronounced among HIV-infected women (Table II.) Among HIV-uninfected women, the total live birth rate per 1000 person-years was only 5% higher in the HAART era than pre-HAART, while for women with HIV, the rate increased by 150% (p=.001.) Results of multivariate analysis are shown in Table II; the p value represents the significance of the change in birth rate between the cohorts by serostatus, for each covariate, after adjusting for age, race/ethnicity, education, exposure category, and CES-D score.

Among HIV-infected women, the live birth rate was higher in the HAART era than it had been pre-HAART in all age categories, with the largest difference (306%) seen among women over

35 years of age. In the pre-HAART era, HIV-infected women had lower live birth rates than HIV-uninfected women in every age category; however in the HAART era, HIV-infected women younger than 30 years of age had higher birth rates compared with HIV-uninfected women, women between age 30–34 had similar birth rates by serostatus, and HIV-infected women age ≥ 35 years had lower birth rates compared with HIV-uninfected women. The difference in birth rate by HIV status was significant only when comparing women with below 25 years of age to those ≥ 35 years.

Large differences in live birth rate between the pre-HAART and HAART era occurred among HIV-infected women with greater than high school level education. Among these most highly educated women, in the pre-HAART era, the birth rate among HIV-infected women was about half that of HIV-uninfected women, while in the HAART era, the rate among HIV-infected women was more than double that of HIV-uninfected women. While an increase in live birth rates in HIV-infected women occurred across all education levels, there was a differential rate of change over time when comparing those with less than high school education to those with greater than high school education ($p=.05$.)

Women with a history of injection drug use were the only group in both the HIV-infected and HIV-uninfected cohorts who experienced a decline in birth rates between the two treatment eras. Although the rates among HIV-infected women with heterosexual exposure risk and those with no identified exposure risk were higher in the HAART era, the birth rate among women with a history of injection drug use was 19% lower. Table III shows the age-adjusted effect of CD4+ count on the live birth rate for HIV-infected women in the pre-HAART and HAART era cohorts. In the pre-HAART cohort, higher CD4+ counts were associated with higher live birth rates, yet in the HAART era, the relationship between CD4+ count and birth rate was non-linear. Within each category of CD4+ lymphocyte count, the birth rate was higher in the HAART era, and the greatest differences in live birth rate were observed in the lowest CD4+ category. CD4+ count was not included in the final Poisson regression model, which included HIV-uninfected controls.

Comment

In a study of HIV-infected and at-risk women recruited before and after HAART became available in the United States, we found that live birth rates were significantly higher in the latter period among HIV-infected women, even after adjusting for several potential confounders. Birth rates remained stable for HIV-uninfected women over time. Among HIV-infected women, the largest difference in live birth rate between the two time periods was seen among older women, and those with a higher level of education. These findings suggest that the availability of effective interventions for the treatment of HIV infection and interruption of maternal to child transmission has markedly influenced the reproductive choices of HIV-infected women in the United States.

Effective therapies have markedly improved the prognosis for HIV-infected women and their infected children, and reductions in the mother-to-child-transmission rate to as low as 1–2% are now achievable^{4, 5}. Studies conducted earlier in the HIV epidemic found that for women living with HIV, serostatus is not the primary influence on pregnancy-related decisions^{8, 9, 13–15}. In several studies, although women expressed concerns about the risk of perinatal transmission of HIV, the strongest influence on the decision to carry a pregnancy to term was the woman's desire for a child^{8, 9, 16}. Yet changing trends in pregnancy outcomes among HIV-infected women have been reported in Europe; in 1987 the abortion percentage exceeded that of delivery (27% delivery vs. 70% termination) but by 1996 there was a 67% delivery rate and a 32% termination rate¹⁷. More recent data from the WIHS showed that conception rates among HIV-infected women remained stable over time while abortion rates fell after HAART

to rates indistinguishable from HIV-negative controls¹⁸. Our data showing the rise in live birth rates in HIV-infected women after the widespread availability of HAART extends this existing literature. Patterns of live births for HIV-infected women in the United States have drastically changed across treatment eras, and in fact likely reflect an under-estimation of the number of pregnancies occurring in HIV-infected women after the diagnosis of infection,

Similarly, in a longitudinal analysis in the U.S. Adult Spectrum of HIV Disease Project, the pregnancy rate in women with HIV was higher in the era of widespread HAART use (1997–2001) compared with the pregnancy rate between 1992–1996¹⁹, although in that study, there was no comparison group of HIV-uninfected women. Hankins et al. found that after publication of the results of zidovudine for prophylaxis for mother-to-child transmission in 1994, pregnancy rates did not increase, but the incidence of elective abortion decreased, and that while the incidence of live birth did not change after 1994, it significantly dropped after HIV diagnosis compared with prior to HIV diagnosis²⁰. In the European Collaborative Study, among a cohort of HIV-infected women identified during pregnancy, an increasing number of live births subsequent to the index pregnancy in recent years was found, and this time-related trend was seen in both black and white women, leading the authors to postulate that all women in the study are likely to be influenced by the availability of HAART²¹. Our data extend the findings of the European Collaborative Study, by investigating the reproductive behaviors of both HIV-infected and at-risk women, and by including women who were not diagnosed with HIV-infection as part of antenatal testing, as well as those who had no prior pregnancies. Additionally, the trend of increasing live births was most notable among older and more highly educated HIV-infected women, suggesting that awareness of the beneficial effects of HAART had greater influence in these subsets of women.

One limitation of our study was that CD4+ count and HIV viral load levels were not available at the time of the births, which occurred prior to study enrollment. It is possible that birth rates were higher for HIV-infected women in the HAART era compared with the pre-HAART cohort because women enrolled during the HAART era were healthier. However, in a separate analysis of HIV-infected women, the change in live births between the pre-HAART and HAART eras was actually greater for the women in the lowest category of CD4+ count. This difference in the rate of change by CD4 group was significant even after adjustment for the age of the women at the time of diagnosis, thus the inclusion of CD4+ count would have likely strengthened our findings. Also, we cannot distinguish between women who became pregnant by choice, and those whose pregnancies were unwanted. However live birth rates reflect an active decision on the part of the pregnant woman to continue pregnancy to term, which we have shown is clearly associated with the availability of HAART. Finally, we did not specifically look at HAART as an independent variable, as the purpose of this study was to evaluate the population effects of the availability of HAART on the reproductive decisions of HIV-infected and at-risk women.

In conclusion, there has been a dramatic increase in live birth rates for HIV-infected women since HAART became widely available. While the nature of pregnancy decision-making in HIV-infected women is complex, the availability of effective interventions to prevent MTC transmission and improve the prognosis of HIV-infected individuals has shown a significant influence on the reproductive decisions of HIV-infected women, favoring continuation of pregnancy.

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