Published in final edited form as:

AIDS. 2011 March 13; 25(5): 707–711. doi:10.1097/QAD.0b013e3283445811.

Relative time to pregnancy among HIV-infected and uninfected women in the Women's Interagency HIV Study, 2002–2009

Beth S. LINAS, MHS,

Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, 615 Wolfe St E6532, Baltimore, MD 21205, 917-536-7535

Howard MINKOFF, MD [Principal Investigator],

Maimonides Medical Center, Department of Obstetrics and Gynecology

Mardge H. COHEN, MD [Principal Investigator],

Chicago WIHS Admin Office & CORE Center

Roksana KARIM, PhD [Statistician],

University of Southern California, Center for Health Professions

Deborah COHAN, MD, MPH [Consortium Site Leader],

San Francisco General Hospital, USCF Dept. of Obstetrics/Gynecology

Rodney L. WRIGHT, MD, MS [Ob/Gyn Clinical Investigator],

Director of HIV Programs, Department of Obstetrics & Gynecology and Women, Albert Einstein College of Medicine

Mary YOUNG, MD [Principal Investigator],

Georgetown University Medical Center

D. Heather WATTS, MD [NICHD Program Officer], and

PAMA/CRMC/NICHD

Elizabeth T. GOLUB, PhD, MPH [Co-Principal Investigator]

WIHS Data Management and Analysis Center, Johns Hopkins School of public health, Department of Epidemiology

Beth S. LINAS: blinas@jhsph.edu

Abstract

Objectives—To determine the incidence rate of, and the relative time to pregnancy by HIV status in US women between 2002 and 2009.

Design—The Women's Interagency HIV Study (WIHS) is an ongoing, multicenter prospective cohort study of the natural and treated history of HIV infection and related outcomes among women with and without HIV.

Methods—Eligible participants were ≥45 years of age; sexually active with male partner(s) or reported a pregnancy outcome within the past year; and never reported hysterectomy, tubal ligation, or oophorectomy. Poisson regression was conducted to compare pregnancy incidence rates over time by HIV status. Relative time to pregnancy was ascertained via Kaplan-Meier plots and generalized gamma survival analysis.

Results—Adjusting for age, number of male sex partners, contraception, parity, exchanging sex, and alcohol use, HIV infection was associated with a 40% reduction in the incidence rate of pregnancy (incidence rate ratio=0.60, 95% confidence interval: [C.I.] 0.46–0.78). The time for HIV-infected women to become pregnant was 73% longer relative to HIV-uninfected women

(relative time=1.73, 95% C.I.: 1.35–2.36). In addition to HIV infection, decreased parity and older age were independent predictors of lower pregnancy incidence.

Conclusions—Despite the beneficial effects of modern antiretroviral therapy on survival and prevention of maternal-to-child transmission, our findings suggest that pregnancy incidence remains lower among HIV-infected women. Whether this lower incidence is due to behavioral differences or reduced biologic fertility remains an area worthy of further study.

Keywords

women; HIV; pregnancy; time to pregnancy; parity

Introduction

Reproductive decision-making for HIV-infected women is complicated [1]. HIV-infected women contend with issues such as unpredictable symptoms, the potential for transmission to the infant, unstable housing, substance abuse and stigma, potentially compromising their perceived ability to become pregnant and/or their parenting abilities [2]. Knowledge regarding differences in pregnancy rates by HIV status may be valuable for HIV-infected women who desire children [3]. Currently there are scant data concerning the relationship between HIV infection and conception [4]. This analysis examined the incidence of pregnancy and the relative time to conception between 2002 and 2009 among HIV-infected and uninfected women enrolled in the Women's Interagency HIV Study (WIHS).

Methods

Study Design

The WIHS is a multicenter prospective cohort study of the natural and treated history of HIV infection among 3,766 women with and without HIV. Details of the WIHS cohort have been previously described; briefly, semiannual study visits include extensive interviews, physical and gynecologic exam, and provision of biologic specimens [5, 6].

Study Population

Eligible women included those who attended at least two WIHS study visits between April 1, 2002 and March 31, 2009; were age 45 at the start of follow-up; reported heterosexual activity and/or a pregnancy outcome within the past year; and never reported hysterectomy, tubal ligation, or oophorectomy. Women reporting use of hormonal and non-hormonal contraceptives were included, as pregnancies were documented among these women. WIHS participants are broadly representative of the HIV-infected female population in the US; they are predominantly African-American, with 50% living below the poverty line, and heterosexual sex is the primary route of HIV exposure [6].

Ascertainment of Exposure and Outcome Variables

The primary exposure, HIV status, was ascertained through serological testing at WIHS enrollment, and subsequent semiannual testing among those HIV-uninfected at enrollment. CD4+ lymphocyte count and plasma HIV RNA were ascertained at each study visit. Pregnancies were self-reported. Participants were asked “have you been pregnant since your last visit?” (yes or no) and “what was the outcome of the pregnancy?”

Assessment of Covariates

Contraceptive use (hormonal and non-hormonal) was self-reported. Parity was defined as the number of previous births (live or stillbirths). Exchanging sex meant trading sex for

drugs, money, or shelter since the prior visit. Drug use, alcohol consumption, depressive symptoms (assessed via the Center for Epidemiologic Studies-Depression Scale (CES-D)) and unstable housing since last visit were also examined as potential confounders [7].

Statistical Analysis

The incidence of pregnancy from 2002–2009 was calculated for the overall sample and stratified by HIV status. Poisson regression compared pregnancy incidence rates by HIV status and predictors thereof.

To compare the time to pregnancy between HIV-infected and uninfected women, a time-to-event analysis was conducted using the Kaplan-Meier method and generalized gamma survival analysis. Person-time accrual began at each participant's first study visit beginning April 1, 2002, and continued until the event (pregnancy), loss to follow-up, or administrative censoring at March 31, 2009 [8].

Bivariate analyses were conducted for each potential confounder; differences by HIV status for categorical variables were assessed via chi-square tests, and the Wilcoxon test compared median values of continuous variables. Variables significantly ($p < 0.05$) associated with both HIV status and pregnancy, as well as known or suspected confounders were included in multivariate analysis; generalized estimating equations adjusted for the correlation of repeated measures. All analyses were conducted using SAS 9.2 (SAS Institute, Cary, North Carolina USA).

Results

A total of 1,412 women (contributing 9,039 person-years) were at risk for becoming pregnant between 2002–2009. Of those, 941 (67%) were HIV-infected and 471 (33%) were HIV-uninfected. Over study follow-up, 456 unique women reported 766 pregnancies.

Demographic characteristics were reported at first visit between 2002–2009 (baseline visit) stratified by HIV status. HIV-infected women were older, with a median age of 34 years (inter-quartile range, IQR, 29–39), than HIV-uninfected women (median 30 years, IQR 23–37; $p < 0.001$). HIV-infected women were more likely than HIV-uninfected women to report being married or living with a partner (38% vs. 25%, respectively); of those never married, 41% were HIV-infected and 52% HIV-uninfected ($p < 0.001$). Two percent of HIV-infected women and 8% of HIV-uninfected women reported exchanging sex since their last visit ($p < 0.001$). Use of any contraceptives in the past 6 months was reported by 84% of HIV-infected and 79% of uninfected women ($p < 0.018$).

The number of male sex partners reported in the past 6 months was statistically different by HIV status ($p < 0.001$). 8% of HIV-infected women and 6% of HIV-uninfected women reported having zero male sex partners; eligibility required at least 1 male partner within the last year. Among HIV-infected women, 80% reported having one male partner in the past 6 months, compared to 53% of HIV-uninfected women, while 12% of HIV-infected women and 41% of uninfected women reported 2 male partners.

Parity among HIV-infected women was statistically different from HIV-uninfected women ($p < 0.001$). Twenty-three percent of HIV-infected women reported having zero prior births (alive or still born) compared to 35% of HIV-uninfected women. Forty-seven percent of HIV-infected and 41% of HIV-uninfected women had 1 or 2 prior births. Twenty-four percent of HIV-infected women reported greater than 3 prior births compared to 30% reported among HIV-uninfected women.

Among HIV-infected women the median viral load at baseline was 540 copies/ml (IQR 80–99,000 cp/ml), and median CD4+ lymphocyte count was 497 cells/ μ L (IQR 298–655). There were 619 (66%) HIV-infected women on antiretroviral therapy and 321 (34%) women not on therapy.

Of the 766 reported pregnancies, 404 (53%) were among HIV-infected women and 362 (47%) among HIV-uninfected women. Additionally, 192 pregnancies occurred at the same visit hormonal contraception was reported. The overall incidence rate of pregnancy was 1.2 per 100 person-years (95% C.I.: 1.1–1.3 per 100 person-years). The incidence rate of pregnancy among HIV-infected women was significantly lower [0.95 per 100 person-years (95% C.I.: 0.86–1.0 per 100 person-years)] than among HIV-uninfected women [1.7 per 100 person-years (95% C.I.: 1.5–1.9 per 100 person-years)].

Table 1 shows the results of the Poisson regression and generalized gamma analyses, adjusted for age, parity, alcohol consumption, exchanging sex, number of male sex partners and contraception use in the past 6 months. HIV infection was associated with a 40% reduction in the incidence rate of pregnancy (Incidence Rate Ratio, IRR=0.60, 95% C.I.: 0.46–0.78). The time for HIV-infected women to become pregnant was 73% longer relative to HIV-uninfected women (Relative Time, RT=1.73 95% C.I.: 1.35–2.36).

Older age was also associated with a reduction in the incidence rate of pregnancy and longer time to first pregnancy (IRR=0.89, 95% C.I.: 0.88–0.91). The relative time to pregnancy was 30% longer (RT=1.3, 95% C.I.: 1.12–1.70).

Women with 2 sex partners in the past 6 months had a 28% lower pregnancy rate (IRR=0.72, 95% C.I.: 0.53–0.94) and 64% longer time to pregnancy (RT=1.64, 95% C.I.: 1.12–2.40) as compared to women with 1 sex partner.

Women with parity 3 births conceived the fastest, with relative time to conception 0.14 (95% C.I.: 0.09–0.21) compared to women with no prior births. The relationship between parity and pregnancy was similar when examining incidence rate ratios. Compared to nulliparous women, women with 3 prior births had an incidence rate of pregnancy that was more than 12 times higher (IRR=12.64, 95% C.I.: 8.33–19.15).

Figure 1 shows the Kaplan-Meier plot of time to first pregnancy by CD4+ count among HIV-infected women. Women with CD4+ counts $\geq$ 350 cells/ μ L experienced statistically significant faster times to pregnancy compared to women with CD4+ counts <350 cells/ μ L (log rank $p < 0.0073$).

Discussion

HIV-infected women had longer times to conception and a lower incidence rate of pregnancy. Independent predictors of lower pregnancy incidence included HIV infection, increased age, greater number of male sex partners, and lower parity.

Despite reporting lower baseline prevalence of contraception (25% versus 75%; $p < 0.001$), women with 2 male sex partners experienced a 28% lower pregnancy incidence than those with <2 partners. This differential in contraception suggests that women with multiple partners may not be protecting themselves against sexually transmitted infections more than women with fewer partners. Reduced pregnancy rates among women with more sexual partners may be the result of these women engaging in sex differently than women with fewer partners, in a way that is not discernable from the data. For example, the definition of “sex” on the WIHS questionnaire includes oral, vaginal and anal sex, while only unprotected

vaginal sex is a risk factor for pregnancy [9]. Lack of data describing frequency of sexual intercourse prevents further exploration of this hypothesis.

Of the 766 reported pregnancies, 192 occurred at the same visit hormonal contraception was reported. Given the high rate of contraception and of pregnancy, it is possible that women are taking “time outs” from contraception, or are not using it effectively. Among women who reported any contraceptive use in the past 6 months at baseline, 32% were HIV-uninfected and 68% were HIV-infected ($p < 0.0001$). The degree to which inconsistent contraceptive use varies by serostatus could contribute to differences in pregnancy incidence. The addition of data concerning measures of adherence to contraceptive use could strengthen this analysis; unfortunately such data are not available in this cohort.

Parity was an independent predictor of both the incidence of pregnancy as well as faster time to pregnancy. As parity increased, the time to first reported pregnancy was faster, regardless of HIV status. However, HIV-infected women consistently had slower times to pregnancy, regardless of parity. Nulliparous women may have included women who did not desire a child and/or women who were unable to become pregnant. There was no way to distinguish between these types of nulliparous women from the data and therefore causality cannot be determined between parity and one’s ability to become pregnant.

HIV-infected women with a low CD4+ lymphocyte count (<350 cells/ μ l) experienced slower times to pregnancy than those with CD4 ≥ 350 cells/ μ l. The reduction of viral replication under HAART has improved the clinical status of HIV-infected women, yet further examination of the prolonged time to pregnancy among relatively immunocompromised women is warranted to determine if this is due to biological or behavioral factors. [3].

To be at risk for pregnancy, both intent and behavior are relevant, as intent without behavior does not lead to conception. Lower pregnancy rates among HIV-infected women could be attributed to behaviors including fewer episodes of unprotected sex or higher rates of contraception use. These analyses did not investigate measures of biologic infertility. However, these results do indicate lower incidence of and longer times to conception among HIV-infected women as compared to uninfected women, particularly HIV-infected women with CD4+ <350 cells/ μ l. Despite slower times to pregnancy, conception is possible for women living with HIV as they have longer life expectancies due to the beneficial effects of modern antiretroviral therapy [10].

Acknowledgments

Data in this manuscript were collected by the Women’s Interagency HIV Study (WIHS) Collaborative Study Group with centers (Principal Investigators) at New York City/Bronx Consortium (Kathryn Anastos); Brooklyn, NY (Howard Minkoff); Washington DC Metropolitan Consortium (Mary Young); The Connie Wofsy Study Consortium of Northern California (Ruth Greenblatt); Los Angeles County/Southern California Consortium (Alexandra Levine); Chicago Consortium (Mardge Cohen); Data Coordinating Center (Stephen Gange). The WIHS is funded by the National Institute of Allergy and Infectious Diseases (U01-AI-35004, U01-AI-31834, U01-AI-34994, U01-AI-34989, U01-AI-34993, and U01-AI-42590) and by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (U01-HD-32632). The study is co-funded by the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute on Deafness and Other Communication Disorders. Funding is also provided by the National Center for Research Resources (UCSF-CTSI Grant Number UL1 RR024131). The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

References

1. Stanwood NL, Cohn SE, Heiser JR, Pugliese M. Contraception and fertility plans in a cohort of HIV-positive women in care. *Contraception*. 2007; 75:294–298. [PubMed: 17362709]

2. Kirshenbaum SB, Hirky AE, Correale J, Goldstein RB, Johnson MO, Rotheram-Borus MJ, et al. "Throwing the dice": pregnancy decision-making among HIV-positive women in four U.S cities. *Perspect Sex Reprod Health*. 2004; 36:106–113. [PubMed: 15306272]
3. Wilson TE, Massad LS, Riester KA, Barkan S, Richardson J, Young M, et al. Sexual, contraceptive, and drug use behaviors of women with HIV and those at high risk for infection: results from the Women's Interagency HIV Study. *AIDS*. 1999; 13:591–598. [PubMed: 10203384]
4. Massad LS, Springer G, Jacobson L, Watts H, Anastos K, Korn A, et al. Pregnancy rates and predictors of conception, miscarriage and abortion in US women with HIV. *AIDS*. 2004; 18:281–286. [PubMed: 15075546]
5. Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, Miotti P, et al. The Women's Interagency HIV Study. WIHS Collaborative Study Group. *Epidemiology*. 1998; 9:117–125. [PubMed: 9504278]
6. Bacon MC, von Wyl V, Alden C, Sharp G, Robison E, Hessel N, et al. The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. *Clin Diagn Lab Immunol*. 2005; 12:1013–1019. [PubMed: 16148165]
7. Golub ET, Latka M, Hagan H, Havens JR, Hudson SM, Kapadia F, et al. Screening for depressive symptoms among HCV-infected injection drug users: examination of the utility of the CES-D and the Beck Depression Inventory. *J Urban Health*. 2004; 81:278–290. [PubMed: 15136661]
8. Cox C, Chu H, Schneider MF, Munoz A. Parametric survival analysis and taxonomy of hazard functions for the generalized gamma distribution. *Stat Med*. 2007; 26:4352–4374. [PubMed: 17342754]
9. Ezeanochie M, Olagbuji B, Ande A, Oboro V. Fertility preferences, condom use, and concerns among HIV-positive women in serodiscordant relationships in the era of antiretroviral therapy. *Int J Gynaecol Obstet*. 2009; 107:97–98. [PubMed: 19666172]
10. Maier M, Andia I, Emenyonu N, Guzman D, Kaida A, Pepper L, et al. Antiretroviral therapy is associated with increased fertility desire, but not pregnancy or live birth, among HIV+ women in an early HIV treatment program in rural Uganda. *AIDS Behav*. 2009; 13 (Suppl 1):28–37. [PubMed: 18389364]

Figure 1. Time to First Pregnancy for HIV Infected women, 2002 to 2009

Kaplan-Meier curves for time to first pregnancy among HIV-infected women, 2002–2009, stratified by CD4+ cell count. Faster times to pregnancy are indicated by curves with lower proportions of women who are pregnancy-free at any visit.

Table 1

Incidence rate ratio and Relative Time to First Pregnancy between 2002–2009*

	Final Poisson Model	Final Generalized Gamma Model
	Incident Rate Ratio (95% C.I.)	Relative Time (95% C.I.)
HIV+	<i>0.60 (0.46,0.78)</i>	<i>1.73 (1.35,2.36)</i>
Age (yrs)	<i>0.86 (0.85,0.88)</i>	<i>1.3 (1.13,1.70)</i>
Exchange Sex since last visit	0.67 (0.34,1.32)	1.10 (0.44,2.11)
Number of Male partners in thepast 6 months		
0–1	ref	ref
2	0.72(0.53,0.96)	1.62 (1.12,2.40)
Parity		
0	ref	ref
1–2	<i>6.49 (4.43,9.50)</i>	<i>0.24 (0.16,0.35)</i>
3	<i>12.63(8.40,19.00)</i>	<i>0.14 (0.09,0.21)</i>

* Models adjusted for all variables listed plus contraception and alcohol consumption

Bold indicates p-value<0.05

Bold +Italic indicates p-value<0.001