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Untangling the Relationship Between Antiretroviral Therapy Use and Incident Pregnancy: A Marginal Structural Model Analysis Using Data From 47,313 HIV-Positive Women in East Africa

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Background: Scale-up of triple-drug antiretroviral therapy (ART) in Africa has transformed the context of childbearing for HIV-positive women and may impact pregnancy incidence in HIV programs.

Methods: Using observational data from 47,313 HIV-positive women enrolled at 26 HIV clinics in Kenya and Uganda between 2001 and 2009, we calculated the crude cumulative incidence of pregnancy for the pre-ART and on-ART periods. The causal effect of ART use on incident pregnancy was assessed using inverse probability weighted marginal structural models, and the relationship was further explored in multivariable Cox models.

Results: Crude cumulative pregnancy incidence at 1 year after enrollment/ART initiation was 4.0% and 3.9% during the pre-ART

and on-ART periods, respectively. In marginal structural models, ART use was not significantly associated with incident pregnancy [hazard ratio = 1.06; 95% confidence interval (CI): 0.99 to 1.12]. Similarly, in Cox models, there was no significant relationship between ART use and incident pregnancy (cause-specific hazard ratio: 0.98; 95% CI: 0.91 to 1.05), but effect modification was observed. Specifically, women who were pregnant at enrollment and on ART had an increased risk of incident pregnancy compared to those not pregnant at enrollment and not on ART (cause-specific hazard ratio: 1.11; 95% CI: 1.01 to 1.23).

Conclusions: In this large cohort, ART initiation was not associated with incident pregnancy in the general population of women enrolling in HIV care but rather only among those pregnant at enrollment. This finding further highlights the importance of scaling up access to lifelong treatment for pregnant women.

Key Words: pregnancy incidence, ART, HIV/AIDS, sub-Saharan Africa

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INTRODUCTION

The massive expansion of HIV prevention, care, and treatment services in sub-Saharan Africa over the past decade has transformed the context of childbearing for women living with HIV in the region. HIV-positive women are living longer, healthier, and more productive lives^{1–3} and, for the first time since the start of the epidemic, face a real opportunity of bearing HIV-negative children.^{4,5} Whether and how these new realities impact pregnancy incidence among women enrolled in HIV programs have important implications for the organization of services and the clinical management of women's health.

Although numerous qualitative and quantitative studies suggest that women on antiretroviral therapy (ART) are reconsidering their pregnancy desires in favor of childbearing,^{6–9} far less is known about the relationship between ART initiation and incident pregnancy. To date, only 2 studies have directly examined whether ART initiation alters pregnancy incidence.^{6,10} Both found that women on ART were more

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likely to experience incident pregnancy than women in pre-ART care but suffered from limited generalizability—the first comprised women who were pregnant at enrollment in HIV care or recently postpartum, and enrolled through prevention of mother-to-child transmission (PMTCT) programs, and the second was limited to a single site in a large African city. Additionally, although these studies provided insights into patient-level factors associated with incident pregnancy, information is needed on whether site-level factors (eg, availability of PMTCT services, location of family planning services) are associated with incident pregnancy.

We used data from a large sample of women of reproductive age receiving HIV services in diverse settings in Kenya and Uganda to estimate the potential influence of ART initiation on the incidence of pregnancy. In addition to offering more generalizable results than previous studies and examining the potential relationship between site-level factors and incident pregnancy, the methods used in this article account for 3 critical factors that directly affect estimation of pregnancy incidence: (1) the propensity to initiate ART, and the resulting longitudinal confounding when examining the causal relationship between ART use and incident pregnancy; (2) prevalent pregnancy (ie, pregnancy at enrollment in HIV care) as a factor associated both with the likelihood of enrollment in HIV care and the likelihood of ART initiation; and (3) the competing events of death and loss to program, both of which occur frequently among patients newly enrolling in care.

METHODS

Study Design and Study Population

We conducted an observational cohort analysis using patient- and site-level data from the East African regional consortium of the International Epidemiologic Databases to Evaluate AIDS collaboration (IeDEA; www.iedea.org). Patient information routinely collected during clinic visits was documented by clinicians on national or clinic-developed clinical encounter forms, entered into on-site databases by data clerks, and transmitted to the IeDEA East African Regional Data Center. We evaluated data from women aged 15 to 49 years not known to have been sterilized or to have had a hysterectomy, who enrolled in HIV care between November 27, 2001 and May 8, 2009, and who made at least 1 clinic visit after enrollment or, if pregnant at enrollment, after delivery. The exact date of database closure differed by site and ranged from March 2008 to May 2009. Site-level data were obtained through a closed-ended facility survey completed by facility staff in late 2009 and were assumed to apply to the entire study period.¹¹ The survey documented the context in which facilities operate and specific services available at each facility. Use of these data for research purposes was approved by institutional review bodies at participating clinics and universities.

Data Management

The study outcome, first incident pregnancy, was defined as the first pregnancy observed for women who were

not pregnant at enrollment in HIV care or the first subsequent pregnancy observed for women who were pregnant at enrollment. Conception dates were used to determine if the incident pregnancy occurred in the pre-ART or on-ART period and were estimated using several pregnancy-related measures available in the databases, including: (1) estimated gestational age at clinic visit (based on physical examination); (2) date of last menstrual period (LMP); (3) estimated or actual date of delivery; and (4) pregnancy status at each clinic visit. When a gestational age was available, the date of conception was calculated by backdating the date at which the pregnancy was detected by the recorded gestational age. When no gestational age was available but a date of delivery was recorded, the pregnancy was assumed to have been carried to term and conception was estimated as occurring 280 days earlier. When neither a gestational age nor a date of delivery was available but a date of LMP was recorded, conception was calculated as occurring 14 days after the LMP. Finally, when only the woman's pregnancy status was recorded at 1 or more visits, we assumed a median gestational age of 147 days at first detection and backdated the date of conception accordingly. The median gestational age of 147 days was based on the gestational age at pregnancy identification among women in facilities that recorded gestational age and/or LMP.

Our primary exposure of interest was therapeutic ART use. ART was defined as triple therapy and was treated as a time-dependent variable in all analyses to account for different levels of risk before and after ART initiation for any given patient. Women were considered eligible for ART based on the criteria that were in place at the time of treatment initiation. Women who initiated triple-therapy ART for PMTCT, discontinued it after delivery and later became pregnant again were classified as *not* on ART at the time of conception. Body weight, World Health Organization (WHO) stage, and CD4 count were among the other patient-level variables of interest in our analyses and subject to missing values. Missing weight, WHO stage, and CD4 count across all visits were imputed by linear interpolation (when 2 values were available) or by carrying forward the last available value (when interpolation was impossible). After these procedures, the proportion of women missing weight, WHO stage, and CD4 count was <2%.

Analysis

Pregnancy-free survival was calculated from enrollment in HIV care (for women who were not pregnant at enrollment) or from the estimated or recorded date of delivery (for women who were pregnant at enrollment in HIV care) until: (1) the time of conception of the first incident pregnancy or (2) the time of the last clinic visit recorded before database closure. Censoring was a result of transfer, death, or loss to follow-up (LTFU); the latter was defined as patients without evidence of transfer or death and with no visits for at least 12 months before database closure for pre-ART patients and 6 months for patients on ART. The crude cumulative incidence of pregnancy and 95% confidence intervals (CIs) were calculated using the nonparametric estimation method of Aalen and

Johansen,¹² with death and LTFU considered as competing events. This approach is preferable to using the complement of the Kaplan–Meier survival estimate or any other model that considers death and LTFU as censoring events because such estimates are upwardly biased; indeed, they do not allow deaths before pregnancy and consequently anticipate additional pregnancies in the death and LTFU groups.^{13,14} The pre-ART cumulative incidence of pregnancy was calculated censoring data at the time of ART initiation. The on-ART cumulative incidence of pregnancy was estimated considering women “at risk” for an incident pregnancy only during the time since ART initiation (left-truncated data).

We assessed the causal effect of ART on pregnancy using stabilized inverse probability weighted marginal structural models that adjusted for potential longitudinal confounding because of initiation of ART. In other words, these models account for the fact that ART may be initiated differentially for various patient subgroups over time, and the very membership in these subgroups may be associated with the likelihood of incident pregnancy. A generalized estimating equation model with a logit link was used to generate the estimated probability of starting ART based on a number of patient-level predictive factors recorded at enrollment and over time, including CD4 count, WHO stage, body weight, pregnancy status, the time of each clinic visit relative to enrollment (expressed as both a linear and a quadratic trend), and the HIV program where the patient was receiving services [the Academic Model Providing Access to Healthcare (AMPATH), www.ampathkenya.org; the MTCT-Plus Initiative, www.icap.columbia.edu; the Infectious Diseases Institute, and Family AIDS Care and Education Services (FACES) Partnership, www.faces-kenya.org]. To examine the robustness of our findings, we compared results from the marginal structural model including all patients to a model that only included women who were pregnant at enrollment in care. Stabilized inverse probability weights were determined following the methods of Cole and Hernán (see Tables S1 and S2, Supplemental Digital Content, <http://links.lww.com/QAI/A795>).¹⁵

As a secondary approach, we conducted an unweighted analysis using unadjusted and multivariable Cox proportional hazard models. Although these are not causal models in the strict sense, we include them to allow “backward compatibility” with previous publications.^{6,10} Patient-level measures of interest included age and pregnancy status at enrollment, enrollment year, and WHO stage, and CD4 count recorded at enrollment and over time. Regarding site-level factors, we included program model, facility location (rural, semi-urban, urban), facility type (teaching/referral hospitals, district hospitals/sub-district hospitals, rural health centers), location of PMTCT services (integrated within the HIV clinic, elsewhere in facility, at another facility), and location of family planning services (integrated within the HIV clinic, elsewhere in the facility). For the multivariable analysis, factors significant at $\alpha = 0.20$ level in unadjusted analyses were added to a model that included ART using a forward stepwise approach and were evaluated for their effect on the risk of incident pregnancy and their confounding effect with ART initiation. We also

included an interaction term to determine whether the relationship of ART and incident pregnancy was modified by pregnancy status at enrollment in care. Factors significant at $\alpha = 0.05$ level were retained in the multivariable model. In the context of the competing risk framework, this model, which censors death and LTFU, estimates cause-specific hazard rates (CSHR).¹⁶

Analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC). Interpolation and imputation of missing data were performed with STATA version 13.0 (Stata Corp, College Station, TX).

RESULTS

Patient and Site Characteristics

Overall, 47,313 women enrolled in HIV care during the study period and met the study eligibility criteria, 10% of whom were pregnant at enrollment (Table 1). Most (86%) were enrolled between 2005 and 2009. At enrollment, women averaged 32.5 years and about one-third were known to be married or living with a partner. Only 4% of women were known to be nulliparous at enrollment, and among those with information on prior births, median parity was 3. Approximately one-third of patients were enrolled with a WHO stage of III/IV and the median CD4 count at enrollment (assessed among 83% of women) was 230 cells per microliter (interquartile range: 99–418). Sixty-one percent of women had initiated ART by the end of the observation period, such that 39% of the women were observed only during the pre-ART period, 8% were observed only on ART, and 53% were observed both before and after ART initiation.

Table 2 shows site-level characteristics of included facilities. Women received care in 26 facilities: 23 in Kenya and 3 in Uganda. Eighteen facilities were part of the AMPATH Consortium, 3 were affiliated with the MTCT-Plus Initiative, 4 were from the FACES Partnership, and the remaining site was not affiliated with a larger program model. Half of the facilities were located in urban areas. Thirteen offered family planning services within the HIV care clinic. PMTCT services were integrated in the HIV clinic in 13 facilities.

Crude Cumulative Incidence of Pregnancy

The cumulative incidence of pregnancy at 1 year from enrollment was 7.0%. The incidence 1 year after enrollment for those in pre-ART care was 4.0% and 1 year after ART initiation for those on ART was 3.9% (Table 3). The cumulative incidence of pregnancy for both the pre-ART and the on-ART periods was highest for women aged 20 years or younger (pre-ART: 8.7%, 95% CI: 6.8 to 11.0; on ART: 9.7%, 95% CI: 6.5 to 14.4) and those who were married or living with a partner (pre-ART: 7.4%, 95% CI: 7.0% to 7.9%; on ART: 5.3%, 95% CI: 4.8% to 6.0%) and had baseline CD4 counts ≥ 350 cells per microliter (pre-ART: 9.1%, 95% CI: 8.6% to 9.7%; on ART: 6.0%, 95% CI: 4.9% to 7.2%). Additionally, the cumulative incidence of pregnancy was higher at 1 year in the pre-ART period

TABLE 1. Sociodemographic and Clinical Characteristics of Study Participants*

	n (%)
No. participants	47,313 (100.0)
Age at enrollment, yr	
Median, IQR	32.5 (27.6–38.6)
Enrollment year	
2001–2004	6403 (13.5)
2005–2006	20,997 (44.4)
2007–2009	19,913 (42.1)
Civil status	
Never married/not living with partner	3749 (7.9)
Married/living with partner	15,187 (32.1)
Divorced/separated	5292 (11.2)
Widowed	8381 (17.7)
Missing	14,704 (31.1)
Number of live births	
Median, IQR	3.0 (2.0–5.0)
0	1698 (3.6)
1–2	12,724 (26.9)
3–4	11,277 (23.8)
≥5	9242 (19.5)
Missing	12,372 (26.2)
Pregnant at enrollment	
Yes	4487 (9.5)
No	42,826 (90.5)
Weight at enrollment, kg	
Median (IQR)	54.0 (47.5–61.0)
WHO stage at enrollment	
I/II	26,278 (55.5)
III/IV	16,330 (34.5)
Missing	4705 (9.9)
CD4 cells per microliter at enrollment	
Median (IQR)	230.0 (99–418)
0–99	9789 (20.7)
100–199	7812 (16.5)
200–349	8816 (18.6)
≥350	12,713 (26.9)
Missing	8183 (17.3)
Initiated ART during study period	
Yes	28,652 (60.6)
No	18,661 (39.4)

*Data do not reflect imputed values.

than in the on-ART period for all subgroups examined, with the exception of the following: nulliparous women, women with low CD4 counts at enrollment (≤ 199 cells/ μ L), and women enrolled at facilities that referred women off-site for PMTCT services.

Factors Associated With Incident Pregnancy

Table 4 shows results from the: (1) marginal structural model weighted for the propensity of ART initiation; (2) unadjusted Cox models; (3) adjusted Cox model; (4) adjusted Cox model with the addition of the interaction term for pregnancy status at enrollment and ART status. The

TABLE 2. Site Characteristics

	n (%)
Number of sites	26 (100.0)
Country	
Kenya	23 (88.0)
Uganda	3 (12.0)
Program	
AMPATH	18 (69.2)
MTCT-plus	3 (11.5)
Infectious Diseases Institute	1 (3.9)
FACES	4 (15.4)
Facility location	
Urban	13 (50.0)
Semi-urban	7 (26.9)
Rural	6 (23.1)
Facility type	
Referral/teaching hospital	4 (15.4)
District hospital	12 (46.2)
Health center	10 (38.5)
Availability of family planning within HIV clinic	
Yes	13 (50.0)
No	13 (50.0)
Availability of PMTCT within facility	
Embedded in HIV clinic	13 (50.0)
Elsewhere in facility	10 (38.5)
Off-site	3 (11.5)

marginal structural model showed a nonsignificant association between ART use and incident pregnancy (adjusted hazard ratio [aHR]: 1.06, 95% CI: 0.99 to 1.12) (column 1). ART use was associated with an 11% lower hazard of incident pregnancy in the unadjusted Cox model (column 2), but no difference was observed after adjustment for other patient-level and site-level variables (CSHR: 0.98, 95% CI: 0.91 to 1.05) (column 3). The addition of an interaction term between pregnancy status at enrollment in HIV care and time-dependent ART status (column 4) showed that the relationship between ART use and incident pregnancy was modified by pregnancy status at enrollment. Relative to women who were not pregnant at enrollment and not on ART, no significant difference was observed in the hazard of pregnancy among women who were not pregnant at enrollment and on ART, whereas women who were pregnant at enrollment and not on ART were significantly less likely to have an incident pregnancy (adjusted cause-specific hazard ratio [aCSHR]: 0.78, 95% CI: 0.61 to 0.98). ART use among women who enrolled when pregnant was associated with an 11% higher hazard of a subsequent pregnancy compared to women who were not pregnant when enrolled and not on ART (aCSHR: 1.11, 95% CI: 1.01 to 1.23). The sensitivity analysis that used a marginal structural model to examine the relationship between ART use and incident pregnancy only among women who were pregnant at enrollment yielded a hazard ratio = 1.31 (95% CI: 0.92 to 1.86).

Regarding other patient-level factors independently associated with incident pregnancy in the adjusted Cox model

TABLE 3. Crude Cumulative Incidence of Pregnancy (and 95% CIs) 1 Year After Enrollment in HIV Care (All Patients), 1 Year After Enrollment in HIV Care (Pre-ART Patients Only), and 1 Year After ART Initiation (ART Patients Only)

	Cumulative Incidence (95% CI)*		
	Overall	Pre-ART Period	On-ART Period
Overall	7.9 (7.6 to 8.2)	4.0 (3.8 to 4.2)	3.9 (1.5 to 4.2)
Patient-level characteristics			
Age at enrollment, yr			
<20	14.2 (11.6 to 17.3)	8.7 (6.8 to 11.0)	9.7 (6.5 to 14.4)
20–29	13.5 (12.9 to 14.2)	9.0 (8.5 to 9.5)	7.0 (6.3 to 7.7)
30–39	6.3 (6.0 to 6.8)	4.1 (3.8 to 4.4)	3.2 (2.9 to 3.6)
40–49	1.4 (1.1 to 1.7)	1.0 (0.8 to 1.2)	0.6 (0.4 to 1.0)
Enrollment year			
2001–2004	5.4 (4.8 to 6.0)	3.8 (3.4 to 4.4)	2.5 (1.9 to 3.1)
2005–2006	8.4 (8.0 to 8.8)	5.4 (5.0 to 5.7)	4.4 (4.0 to 4.9)
2007–2009	8.2 (7.7 to 8.7)	5.5 (5.1 to 5.9)	3.6 (3.1 to 4.1)
Education level			
None	5.4 (3.9 to 7.4)	3.9 (2.6 to 5.6)	2.4 (1.2 to 4.7)
Primary level	9.8 (9.3 to 10.3)	6.3 (5.9 to 6.7)	4.9 (4.4 to 5.4)
Secondary level	7.3 (6.7 to 7.9)	4.7 (4.3 to 5.2)	3.5 (2.9 to 4.1)
Tertiary level	6.7 (5.5 to 8.2)	4.7 (3.6 to 5.8)	2.8 (1.9 to 4.3)
Civil status			
Never married/not living with partner	6.7 (5.7 to 7.9)	4.7 (4.0 to 5.6)	2.7 (1.9 to 3.9)
Married/living with partner	11.5 (10.9 to 12.1)	7.4 (7.0 to 7.9)	5.3 (4.8 to 6.0)
Divorced/separated	6.7 (5.9 to 7.6)	4.1 (3.5 to 4.7)	3.6 (2.8 to 4.5)
Widowed	4.2 (3.7 to 4.7)	2.8 (2.4 to 3.3)	2.0 (1.6 to 2.6)
Number of live births			
0	10.1 (8.5 to 12.1)	5.1 (4.0 to 6.4)	6.1 (4.5 to 8.3)
1–2	9.9 (9.3 to 10.6)	6.3 (5.8 to 6.8)	4.8 (4.3 to 5.5)
3–4	9.3 (8.6 to 9.9)	6.0 (5.5 to 6.5)	4.5 (3.9 to 5.2)
≥5	5.8 (5.2 to 6.3)	4.1 (3.7 to 4.6)	2.6 (2.1 to 3.2)
Pregnant at enrollment			
Yes	14.1 (12.9 to 15.3)	4.6 (4.0 to 5.2)	6.6 (5.8 to 7.6)
No	7.2 (6.9 to 7.5)	5.3 (5.0 to 5.5)	3.4 (3.1 to 3.7)
CD4 cells per microliter at enrollment			
0–99	6.2 (5.6 to 6.8)	2.2 (1.9 to 2.5)	3.9 (3.5 to 4.5)
100–199	6.9 (6.3 to 7.5)	3.1 (2.9 to 3.7)	3.7 (3.2 to 4.3)
200–349	7.9 (7.3 to 8.6)	6.2 (5.7 to 6.8)	3.2 (2.5 to 4.0)
≥350	11.0 (10.4 to 11.7)	9.1 (8.6 to 9.7)	6.0 (4.9 to 7.2)
Site-level characteristics			
Program			
AMPATH	8.4 (8.1 to 8.8)	5.5 (5.2 to 5.7)	4.2 (3.8 to 4.5)
MTCT-plus	9.7 (8.1 to 11.6)	7.5 (6.1 to 9.1)	2.7 (2.2 to 3.4)
Infectious Diseases Institute	5.1 (4.6 to 5.8)	3.2 (2.7 to 3.7)	3.2 (1.8 to 5.4)
FACES	7.0 (6.2 to 8.0)	5.3 (4.7 to 6.2)	3.8 (2.7 to 5.4)
Facility location			
Urban	8.7 (7.9 to 9.5)	5.8 (5.2 to 6.5)	4.4 (3.6 to 5.3)
Semi-urban	8.1 (7.6 to 8.7)	5.3 (4.9 to 5.8)	4.0 (3.5 to 4.6)
Rural	8.2 (7.8 to 8.7)	5.4 (5.0 to 5.7)	4.2 (3.7 to 4.7)
Facility type			
Referral/teaching hospital	7.0 (6.6 to 7.5)	4.6 (4.3 to 5.0)	3.3 (2.9 to 3.7)
District hospital	9.3 (8.7 to 9.9)	6.1 (5.7 to 6.6)	4.4 (3.9 to 5.0)
Health center	7.5 (7.1 to 8.0)	5.0 (4.6 to 5.3)	4.1 (3.6 to 4.7)
Availability of PMTCT within facility			
Embedded in HIV clinic	8.4 (7.9 to 8.9)	5.6 (5.2 to 6.0)	4.2 (3.7 to 4.7)
Elsewhere in facility	8.2 (7.7 to 8.7)	5.3 (5.0 to 5.7)	4.1 (3.7 to 4.6)
Off-site	6.6 (4.2 to 0.3)	4.1 (2.1 to 6.9)	4.8 (2.3 to 9.8)

*At 12 months after enrollment (pre-ART period) or 12 months after ART initiation (among women with no previous incident pregnancies who started ART).

TABLE 4. Inverse Probability Weighted, Unadjusted, and Adjusted Hazard of Incident Pregnancy (n = 47,313 Women)

	Column 1: Marginal Structural Model Weighted for ART Initiation Propensity		Column 2: Unadjusted Unweighted Cox Models		Column 3: Adjusted Unweighted Cox Model; No Interaction Term		Column 4: Adjusted Unweighted Cox Model With Interaction Term for Pregnancy Status at Enrollment in HIV Care and ART Use	
	aHR	95% CI	CSHR	95% CI	aCSHR	95% CI	aCSHR	95% CI
Patient-level factors								
Age at enrollment (yr, per additional year)	0.90	0.90 to 0.91	0.90	0.90 to 0.91	0.90	0.90 to 0.90	0.90	0.90 to 0.91
Enrollment year								
2001–2004			1.00	Reference	1.00	Reference	1.00	Reference
2005–2006			1.19	1.11 to 1.27	1.25	1.15 to 1.36	1.25	1.15 to 1.36
2007–2009			1.14	1.04 to 1.25	1.07	0.96 to 1.20	1.07	0.95 to 1.20
CD4 ⁺ (cells/ μ L) (time dependent)								
0–99			1.00	Reference	1.00	Reference	1.00	Reference
100–199			0.98	0.86 to 1.12	0.95	0.83 to 1.09	0.95	0.83 to 1.09
200–349			0.99	0.87 to 1.11	0.90	0.79 to 1.02	0.89	0.78 to 1.02
\geq 350			1.25	1.11 to 1.40	0.90	0.79 to 1.02	0.89	0.78 to 1.01
WHO stage (time dependent)								
I/II			1.00	Reference	1.00	Reference	1.00	Reference
III/IV			0.68	0.64 to 0.72	0.81	0.75 to 0.87	0.81	0.76 to 0.87
Weight at enrollment (kg, per additional 5 kg)			1.00	0.98 to 1.01	0.99	0.98 to 1.01	0.99	0.98 to 1.01
Pregnant at enrollment in HIV care								
No			1.00	Reference	1.00	Reference		
Yes			1.98	1.83 to 2.13	1.10	0.99 to 1.21		
On ART (time dependent)								
No	1.00	Reference	1.00	Reference	1.00	Reference		
Yes	1.06	0.99 to 1.12	0.89	0.84 to 0.94	0.98	0.91 to 1.05		
Pregnancy status at enrollment in HIV care \times ART status (time-dependent)								
Not pregnant at enrollment in HIV care and not on ART							1.00	Reference
Not pregnant at enrollment in HIV care and on ART							0.94	0.88 to 1.02
Pregnant at enrollment in HIV care and not on ART							0.78	0.61 to 0.98
Pregnant at enrollment in HIV care and on ART							1.11	1.01 to 1.23
Site-level factors								
Program								
AMPATH			1.00	Reference	1.00	Reference	1.00	Reference
MTCT-plus			1.40	1.25 to 1.57	0.87	0.76 to 1.00	0.92	0.80 to 1.06
Infectious Diseases Institute			0.77	0.71 to 0.83	0.89	0.80 to 0.98	0.90	0.81 to 0.99
FACES			0.90	0.81 to 1.01	0.88	0.73 to 1.07	0.89	0.73 to 1.08
Facility type								
Referral/teaching hospital			1.00	Reference	1.00	Reference	1.00	Reference
District/sub-district hospital			1.19	1.11 to 1.27	1.14	1.05 to 1.24	1.15	1.06 to 1.25
Health center			1.00	0.94 to 1.07	1.00	0.92 to 1.09	1.01	0.92 to 1.10

(column 4), patients enrolling in HIV care in 2005–2006 relative to the very early phase of HIV service scale-up (2001–2004) were more likely to have an incident pregnancy, whereas those with WHO Stage III/IV vs. I/II were less likely to experience an incident pregnancy. With respect to site-level factors, relative to women enrolled at AMPATH, those

enrolled at the Infectious Diseases Institute had a decreased risk of incident pregnancy, whereas those in the MTCT-Plus Initiative, most of whom were pregnant at enrollment, had a significantly higher risk of incident pregnancy. In addition, women enrolled at district/subdistrict hospitals had an increased risk of incident pregnancy compared to those

enrolled at tertiary-level facilities. On-site availability of PMTCT services and integration of family planning services in the HIV care clinic were not significantly associated with incident pregnancy in unadjusted or adjusted analyses.

DISCUSSION

In this study, conducted in its entirety before the roll out of PMTCT option B+, we examined data from a cohort of 47,313 HIV-positive women at 26 HIV clinics in Kenya and Uganda and found that the relationship between ART initiation and incident pregnancy is nuanced and substantially weaker than previously reported. Whereas the 2 previous studies that included patients both in pre-ART care and on-ART reported an increased incidence of pregnancy following ART initiation,^{6,10} in our study, this relationship was not observed when we conducted a more rigorous causal analysis using marginal structural models and observed only among the subset of women who were pregnant at enrollment in HIV care in our secondary analysis that used similar methods to those used in the previous studies. Of note, one of these earlier studies comprised women who were pregnant or recently postpartum at enrollment in HIV care,¹⁰ whereas the other did not examine the potential effect modification by baseline pregnancy status.⁶ One possible explanation for an increased likelihood of incident pregnancy while on ART among women who were pregnant at enrollment in HIV care is that pregnancies at enrollment represent a large number of factors that predispose women to both ART initiation (as pregnant women are more likely to be identified by and subsequently enroll in HIV programs) and incident pregnancy (as women who are pregnant at enrollment have demonstrated the ability, desire, and/or availability of the proper environment to get pregnant). Analyses conducted to generate the weights for the marginal structural models show that women who were pregnant at enrollment were substantially more likely to be initiated on ART than women who were not pregnant at enrollment (see Tables S1 and S2, Supplemental Digital Content, <http://links.lww.com/QAI/A795>). Additionally, women who were pregnant at enrollment in HIV care may have received PMTCT services during their previous pregnancy and thus have increased knowledge of the prevention benefits of ART, which in turn may have affected their subsequent pregnancy intentions. Indeed, HIV-positive women in Zambia who knew of PMTCT drugs and believed they were effective were more likely to desire children than HIV-positive women without such knowledge.¹⁷ Taken together, these findings suggest that previous analyses may not have adequately adjusted for the salient effect of prevalent pregnancy in and of itself on enrollment in care, ART initiation, and incident pregnancy.

In our study, the crude cumulative pregnancy incidence at 1 year was 4.0% during the pre-ART period and 3.9% during the on-ART period. Although not directly comparable, the cumulative incidence 1 year after enrollment in the pre-ART period seems lower than the incidence

rate reported by Myer et al¹⁰ from a multi-country study (6.5 per 100 WY), and substantially lower than that reported from a single site in Kampala, Uganda when pregnancy tests were used (13.1 per 100 WY).⁶ Among patients on ART, more data are available for comparison and suggest that the cumulative incidence of 3.9% at 1 year after ART initiation observed in our study is lower than the incidence rates reported in other studies from Eastern and Southern Africa, which range from 5.2 to 9.4 per 100 WY in the absence of pregnancy testing,^{8,10,18} and is much lower than that reported when pregnancy testing was used (21.6–24.5 per 100 WY).^{6,9} Of note, however, incidence rates reported in other studies are subject to potentially significant upward bias as they do not take into consideration the competing events of death and LTFU. Pregnancy incidence rates calculated with our data for the pre-ART and on-ART periods (8.6 and 6.7 pregnancies per 100 WY, respectively; data not shown) were substantially higher than the cumulative pregnancy incidence that we focus on in this analysis.

With regards to site-level determinants, relative to the AMPATH Consortium, pregnancy incidence was lower among patients at the Infectious Diseases Institute, higher among MTCT-Plus sites, and comparable at FACES sites. This likely reflects differences in program models. The MTCT-Plus Initiative specifically targeted pregnant or recently postpartum women, whereas the Infectious Diseases Institute is a referral center that does not specifically follow pregnant women, and FACES is a routine clinical care program similar to AMPATH. Surprisingly, neither the availability of family planning services within the HIV clinic nor ready access to PMTCT services within the health facility was associated with incident pregnancy. This may reflect that incident pregnancy is largely influenced by individual characteristics and behaviors, but it is also possible that the level of service integration was insufficient to influence women's reproductive behaviors and outcomes. Indeed, a 2013 review of studies examining integration of family planning and HIV services reported weak implementation of the intended integration model in the studies from "real-world" settings,¹⁹ and a recent study conducted at one of the facilities included in our analysis showed that unmet need for family planning remained high even when contraceptives were provided in the HIV clinic.²⁰

This study has several important strengths. With data on nearly 50,000 women with more than 5200 incident pregnancies in 26 HIV clinics in 2 countries with substantial HIV epidemics, it is among the largest assessments of the impact of ART initiation on pregnancy incidence. Additionally, we used several analytic approaches to assess the impact of ART initiation on the likelihood of incident pregnancy, including accounting for longitudinal confounding between factors that are associated with the likelihood of initiating ART and are affected themselves by exposure to ART, and examining potential effect modification by pregnancy status at enrollment in HIV care. This multi-pronged approach provides a more nuanced understanding of the relationship between ART use and pregnancy

incidence. We also examined site-level factors associated with pregnancy incidence, which have not been examined previously in relation to incident pregnancy but have been found to be important determinants of other patient outcomes in HIV clinics.^{21–24}

Several limitations should also be noted. First, we lacked data on pregnancy desires, which was an important predictor of incident pregnancy among women enrolled in HIV care in a previous analysis.⁶ Similarly, marital status and parity, important predictors of fertility in the general population, were unavailable for many patients in our study and could not be included in models examining predictors of incident pregnancy. However, inclusion of pregnancy status at enrollment in HIV care allowed us to account for some potential confounding because of reproductive history. Additionally, site-level factors were assessed in 2009 but were assumed to have applied to the entire period extending from 2001 to 2009. Given the intensive scale-up of HIV services during that period, it is likely that services became more comprehensive and integrated over time. For example, clinics that had integrated PMTCT and HIV care and treatment services by 2009 may not have had PMTCT services available at all on-site in 2001. Such misclassification may have attenuated the true association between site-level factors and incident pregnancy. Furthermore, site-level variables did not assess use or coverage of PMTCT and family planning services but rather their availability.

CONCLUSIONS

In conclusion, among a large cohort of women enrolling in HIV care in Kenya and Uganda between 2001 and 2009, we found little evidence that ART initiation is associated with an increased risk of pregnancy in the general population of women enrolling in HIV care. The high incidence of pregnancy we observed both before and after ART initiation underscores the critical importance of enhancing access to reproductive health services for all women in HIV care, regardless of ART status. For women who wish to avoid or delay pregnancy, this entails ensuring access to effective contraceptives, whereas for women who desire children, efforts should focus on promptly ART initiation. Additionally, given the sizable number of women who were pregnant at enrollment in our study, and the elevated risk of incident pregnancy in this group, our findings provide further evidence of the importance of scaling up access to lifelong treatment for pregnant women. Future research should examine whether increased access to Option B+ changes patterns of incident pregnancy among women engaged in HIV care.

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