



OPEN ACCESS

Citation: Ross J, Edmonds A, Hoover DR, Shi Q, Anastos K, Lelo P, et al. (2018) Association between pregnancy at enrollment into HIV care and loss to care among women in the Democratic Republic of Congo, 2006-2013. PLoS ONE 13(4): e0195231. https://doi.org/10.1371/journal.pone.0195231

Editor: Pascal Nji Atanga, Cameroon Baptist Convention Health Services, CAMEROON

Received: July 11, 2017

Accepted: March 8, 2018

Published: April 2, 2018

Copyright: © 2018 Ross et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: Data cannot be openly shared due to the legal restrictions of The Principles of Collaboration in place by the Central Africa International epidemiologic Databases to Evaluate AIDS (https://www.iedea.org/). To request data, qualified researchers may submit the concept sheet found at the following link: https://www.iedea.org/wp-content/uploads/2017/05/IeDEA_Multiregional_Concept_Application_Form_August_2016.docx to https://www.iedea.org/. The authors declare the following special access privileges:

RESEARCH ARTICLE

Association between pregnancy at enrollment into HIV care and loss to care among women in the Democratic Republic of Congo, 2006-2013

Jonathan Ross^{1©}*, Andrew Edmonds^{2©}, Donald R. Hoover^{3©}, Qiuhu Shi^{4©}, Kathryn Anastos^{1©}, Patricia Lelo^{5‡}, Frieda Behets^{2‡}, Marcel Yotebieng^{6©}

- 1 Department of Medicine, Division of General Internal Medicine, Department of Medicine, Albert Einstein College of Medicine / Montefiore Medical Center, Bronx, NY, United States of America, 2 Department of Epidemiology, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, NC, United States of America, 3 Department of Statistics and Biostatistics, Rutgers University, New Brunswick, NJ, United States of America, 4 Department of Epidemiology and Community Health, New York Medical College, Valhalla, NY, United States of America, 5 Kalembelembe Pediatric Hospital, Kinshasa, The Democratic Republic of Congo, 6 College of Public Health, Division of Epidemiology, The Ohio State University, Columbus, OH, United States of America
- These authors contributed equally to this work.
- ‡ These authors also contributed equally to this work.
- * joross@montefiore.org

Abstract

Background

Loss to care is high among asymptomatic HIV-infected women initiated on antiretroviral therapy (ART) during pregnancy or in the postpartum period. However, whether pregnancy itself plays a role in the high loss to care rate is uncertain. We compared loss to care over seven years between pregnant and non-pregnant women at enrollment into HIV care in the Democratic Republic of Congo (DRC).

Methods

We conducted a retrospective analysis of all ART-naive women aged 15–45 initiating HIV care at two large clinics in Kinshasa, DRC, from 2007–2013. Pregnancy status was recorded at care enrollment. Patients were classified as having no follow-up if they did not return to care after the initial enrollment visit. Among those with at least one follow-up visit after enrollment, we classified patients as lost to care if more than 365 days had passed since their last clinic visit. We used logistic regression to model the association between pregnancy status and no follow-up, and Cox proportional hazards regression to model the association between pregnancy status and time to loss to care.

Results

Of 2175 women included in the analysis, 1497 (68.8%) were pregnant at enrollment. Compared to non-pregnant women, pregnant women were less likely to be over 35 years of age



Their study team had access to a larger data set from which the minimal data set was derived.

Thus, they had the ability to cross-check certain variables against other data. All analyses were conducted using the minimal dataset that will be available to researchers making a request to access it.

Funding: This study was conducted as part of the Central Africa International Epidemiologic Databases to Evaluate AIDS (CA-IeDEA) consortium, which is funded by the National Institute of Allergy and Infectious Diseases (https://www.niaid.nih.gov, grant number U01 AI096299 to KA), and received additional support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (https://www.nichd.nih.gov, grant number R01 HD087993) and National Institute of Mental Health grant K23 MH114752 to JR. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

(19.1% vs. 31.9%, p<0.0001) and less likely to be in WHO stage III or IV (9.0% vs. 26.3%, p<0.0001). Among pregnant women, 106 (7.1%) were not seen after enrollment, versus 25 (3.7%) non-pregnant women (adjusted odds ratio 2.01, 95% CI 1.24–3.24). Of the 2,044 women with at least one follow-up visit, 46.5% of pregnant women and 46.7% of non-pregnant women were lost to care by 5 years; hazards of loss to care were similar for pregnant and non-pregnant women (adjusted hazard ratio 1.08, 95% CI 0.93–1.26).

Conclusions

In this large cohort of HIV-infected women, patients pregnant at care enrollment were more likely to never return for follow-up. Among those who attended at least one follow-up visit, loss to care was not different between pregnant and non-pregnant women, suggesting that pregnancy itself may not be the main driver of the high attrition observed in this cohort.

Introduction

Of 1.4 million pregnant women living with HIV globally, over 90% reside in sub-Saharan Africa [1, 2]. Without any intervention, 20–45% of pregnant women will transmit HIV to their infants during pregnancy, labor/delivery, or breastfeeding [3]. Antiretroviral therapy (ART) use during pregnancy and breastfeeding dramatically reduces mother-to-child HIV transmission and improves women and infant outcomes [4, 5]. The past decade has seen enormous scale up of prevention of mother-to-child HIV transmission (PMTCT) services in sub-Saharan Africa, including ART access [6]. However, suboptimal retention of pregnant women along the PMTCT cascade exists, with up to 48% of women not retained through 6 months post-delivery [7–9]. Under World Health Organization (WHO) guidelines recommending lifelong combination ART for all pregnant and breastfeeding HIV infected women, referred to as Option B+ [10], about a sixth of pregnant women initiating ART do not return for a follow-up visit and overall loss to care of women initiating HIV care when pregnant remains high [11–13].

Uncertainty exists about factors driving high loss to care among pregnant women initiating HIV care. Compared to non-pregnant women, pregnant women initiating HIV care are younger and have less advanced HIV disease [14], factors that have been associated with poor retention [15, 16]. After adjusting for these characteristics, multiple large investigations still reported greater loss to care among pregnant women [11–13, 17]. However, interpreting these findings is difficult as different ART eligibility criteria exist for pregnant and non-pregnant women in these studies. Few studies have compared retention in care of pregnant and non-pregnant women before implementation of the 2013 WHO guidelines; those investigations only included patients initiating ART. It is therefore unclear whether the high loss to care observed among pregnant versus non-pregnant women in these studies resulted from lack of patient readiness to start ART, or factors secondary to pregnancy itself.

Most sub-Saharan Africa nations have already adopted Option B+, and nearly all are beginning to provide ART to all people living with HIV regardless of CD4 count. Understanding whether pregnancy at care enrollment is a main predictor of the loss to care observed following the implementation of Option B+ is essential to developing and targeting interventions aimed at maintaining the broader population of people living with HIV in care. This study's goal was thus to compare loss to HIV care by pregnancy status at enrollment at two sites in the Democratic Republic of Congo (DRC) from 2007–2013, a period prior to implementation of lifelong



ART for pregnant and breastfeeding women living with HIV. We hypothesized that women who were pregnant at enrollment would have increased loss to care compared to women who were not pregnant.

Methods

We performed a retrospective cohort study of women living with HIV enrolling in HIV care from 2007–2013 at two sites in Kinshasa, DRC that are affiliated with the Central Africa International Epidemiologic Databases to Evaluate AIDS (CA-IeDEA) Consortium. CA-IeDEA is a multi-country project that collects secondary data from patients receiving HIV care and treatment in the Central African region. Patient data from sites participating in CA-IeDEA are deidentified at the clinic level prior to entry in the cohort database. All research was conducted according to the principles of the Declaration of Helsinki and approved by the Kinshasa School of Public Health Ethics Committee and the Institutional Review Board of the Albert Einstein College of Medicine, both of which waived written or verbal patient consent because the data were de-identified prior to analysis.

Setting

Data were collected at two comprehensive HIV care programs serving patients at Kalembelembe Pediatric Hospital (KLL) and Bomoi Healthcare Center (BHC) in Kinshasa, DRC [18, 19]. The DRC is a large, Central African country with a population of over 80 million and an overall HIV prevalence of 0.8% [20]. An estimated 200,000 Congolese women aged 15–49 are HIV-infected. Up to 15% of pregnancies among HIV-infected women result in HIV transmission to infants [20]. From 2013 Demographic and Health Surveys in DRC [21], roughly 9 in 10 mothers in DRC and 96% in Kinshasa attended at least one antenatal care visit before their most recent delivery. Breastfeeding is virtually universal in DRC; 9 out of 10 infants still breastfeed at 1 year [22, 23]. From its origins in the early 2000s until 2010, the DRC PMTCT program was based on provision of a single intra-partum dose of nevirapine, with the addition of daily AZT/3TC until 7 days postpartum recommended starting in 2006 [24, 25]. Option A–the provision of zidovudine starting as early as 14 weeks through delivery for women ineligible for ART [26]—was introduced in 2009 and fully implemented in DRC by 2010; this remained the standard of care until the implementation of Option B+ in 2015.

Population and clinical procedure

We included all ART-naïve women aged 15–45 years who enrolled in HIV care from January 1, 2007 through July 31, 2013. Women were diagnosed with HIV at the two sites or referred to these sites from affiliated PMTCT sites. Patients enrolled into HIV care at their first post-diagnosis visit at KLL or BHC. At this visit, data were collected on pregnancy status, weight, age, WHO clinical stage, and CD4 count. Decisions to start ART were based on WHO clinical stage (III or IV), CD4 count (≤200 cells/mm³ prior to 2010 or ≤350 cells/mm³ after 2010) or provider discretion. Pregnant women ineligible for ART received either a single intrapartum dose of nevirapine with or without daily AZT/3TC until 7 days postpartum (from 2007–2009), or a regimen of zidovudine during pregnancy (2010–2013) and were considered not to have used ART. Scheduled follow-up differed by calendar period and whether or not patients had initiated ART. From 2007–2009, patients on ART were typically scheduled for monthly visits, and patients not on ART were typically seen quarterly. In subsequent years, patients on ART were initially seen monthly, but once stable on ART were scheduled quarterly; those not on ART were seen biannually. Though tracking practices were not uniform throughout the study



period, typically, for patients who did not attend scheduled visits, up to three phone contacts were attempted, followed by a home visit.

Outcomes and predictor variables

Two primary outcomes were considered in this analysis: no follow-up and loss to care. Patients were classified as having no follow-up if they did not return to care after the initial enrollment visit, and were not included in analyses of loss to care. We defined loss to care as an interval of more than 365 days since last clinic visit to avoid misclassification among patients scheduled for infrequent (biannual) visits. In a sensitivity analysis, we also examined loss to care using a definition of 182 days since last clinic visit. Other covariates included: ART initiation within three months of enrollment (yes or no); pregnancy status; baseline age (categorized as 15–24, 25–34, or 35–45 years at enrollment); baseline CD4 count (classified as <200, 201–350, or >350 cells/mm³); and WHO clinical stage (I or II, III or IV, missing) each of these obtained at any visit up to 30 days after enrollment.

Statistical analyses

Baseline characteristics of pregnant and non-pregnant women were compared using chisquare tests for categorical and Mann-Whitney tests for continuous variables. For the outcome of no follow-up, we used bivariate and multivariable logistic regression models respectively to generate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) comparing proportions of women with no follow-up after enrollment by pregnancy status at enrollment. For those who returned for at least one post-enrollment visit, Kaplan-Meier survival analyses were used to compare proportions of pregnant and non-pregnant women lost to care over follow-up time. We then used Cox proportional hazard models to generate hazard ratios (HRs) with 95% CIs comparing loss to care by pregnancy status at enrollment. For these analyses, patients were censored at the date of their last clinic visit (if they had one of the following events: lost to care, died, or transferred clinics) or 365 days before the database closing date of August 1, 2013 (if they did not have an event). We also conducted a sensitivity analysis exploring whether the association between pregnancy status at enrollment and loss to care differed when limiting follow-up time to the first 2 years after enrollment, when pregnancy might be expected to have the strongest effect. For this analysis, we utilized a 182-day loss to care definition and censored patients who did not have an event by 24 months after their enrollment date. Data were analyzed using SAS 9.3 (SAS Institute Inc., Cary, NC). Statistical significance was two-sided at p<0.05.

Results

Of the 2175 women enrolled in care at the two clinics from 2007 through 2013, 982 (45.1%) enrolled from 2007–2009 and 1173 (54.9%) from 2010–2013. At enrollment, 1497 (68.8%) were pregnant, median age was 30 years (interquartile range [IQR] 26–34), and 312 (14.3%) were in WHO clinical stage III or IV (Table 1). Median CD4 count at enrollment was 356 cells/mm³ (IQR 215–534). A total of 131 patients (6.0%) did not return after the enrollment visit.

Compared to non-pregnant women, pregnant women at enrollment were less likely to: be over 35 years of age (19.1% vs. 31.9%, p<0.0001), enroll in care during 2010–2013 compared to 2007–2009 (49.7% vs. 68.4%, p<0.0001), and be in WHO clinical stage III or IV (9.0% vs. 26.3%, p<0.0001). Notably, baseline CD4 counts did not statistically differ between the two groups (p = 0.31).



Table 1. Baseline demographic and clinical characteristics of HIV-infected women who received care at Kalembelembe Pediatric Hospital and Bomoi Healthcare Center in Kinshasa, DRC, 2007–2013 (N = 2175).

Characteristic	Total (n = 2175)	Pregnant (n = 1497)	Not pregnant (n = 678)	P
Year of enrollment, n (%)				<0.0001^
2007–2009	982 (45.1)	768 (51.3)	214 (31.6)	
2010–2013	1193 (54.9)	729 (49.7)	464 (68.4)	
Age, n (%)				<0.0001^
15–24	372 (17.1)	273 (18.2)	99 (14.6)	
25–34	1301 (59.8)	938 (62.7)	363 (53.5)	
35–45	502 (23.1)	286 (19.1)	216 (31.9)	
WHO clinical stage, n (%)				<0.0001^
Stage I or II	1848 (85.0)	1351 (90.2)	497 (73.3)	
Stage III or IV	312 (14.3)	134 (9.0)	178 (26.3)	
Missing	15 (0.7)	12 (0.8)	3 (0.4)	
CD4 count, median cells/mm ³ (IQR)	356 (215–534)	349 (224–515)	366 (196–574)	0.31
ART initiated within 3 months of enrollment, n (%)	802 (36.9)	506 (33.8)	296 (43.7)	<0.0001^
Median years of follow-up (IQR)	4 (3-6)	4 (3-5)	5 (3-6)	<0.0001
No follow-up after enrollment, n (%)	131 (6.0)	106 (7.1)	25 (3.7)	<0.0001
Lost to care, n (%)*	860 (42.1)	572 (41.0)	288 (43.8)	0.60^
Transferred to another facility	32 (1.5)	21 (1.4)	11 (1.6)	0.69^
Died	91 (4.2)	56 (3.7)	35 (5.2)	0.13^

DRC = Democratic Republic of Congo.

IQR = interquartile range.

WHO = World Health Organization.

ART = antiretroviral therapy.

https://doi.org/10.1371/journal.pone.0195231.t001

Among 2,044 patients who returned for at least one visit after enrollment, 865 (42.3%) were eligible for ART at enrollment based on CD4 count and/or WHO stage, of whom 660 (76.3%) started ART within 3 months (**Fig 1**). An additional 142 patients initiated ART within 3 months of enrollment, and another 465 patients initiated ART beyond 3 months. In total, 1267 patients (58.3%) initiated ART during the follow-up period. Among patients meeting CD4 and/or WHO stage criteria for ART initiation, similar proportions of pregnant and non-pregnant women initiated ART within three months after enrollment into care (75.0% vs 78.6%, p = 0.23).

No follow-up

Of 1497 pregnant women enrolled in HIV care, 106 (7.1%) were not seen after enrollment, compared to 25 (3.7%) of 678 non-pregnant women (OR comparing pregnant to non-pregnant women 1.99, 95% CI 1.27–3.11), p<0.01). In logistic regression analysis adjusted for year of enrollment, age at enrollment, baseline CD4 count, and WHO clinical stage, pregnant women were about twice as likely not to be seen after enrollment (adjusted OR 2.11, 95% CI 1.24–3.24) (Table 2).

Loss to care

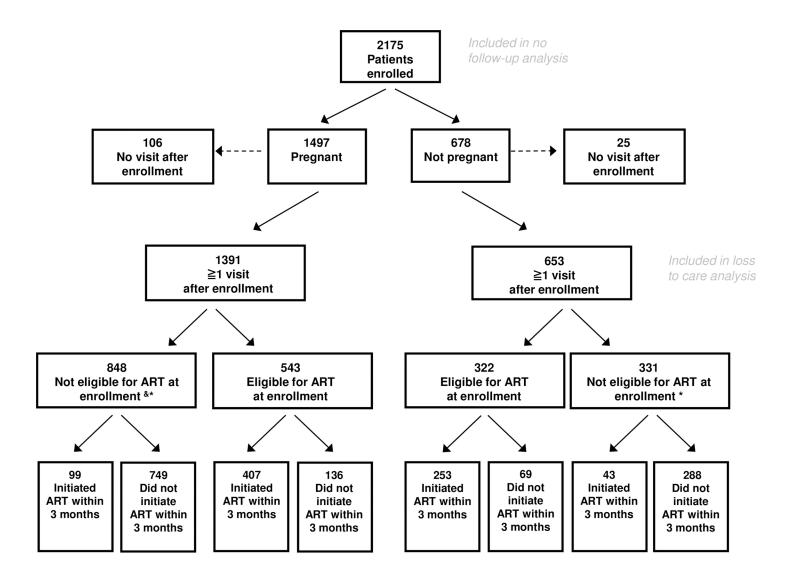
We included the 2044 women who returned for at least one post-enrollment visit in the analysis of loss to care (Fig 2). Median follow-up time among those patients was 4.5 years (IQR 3.0–

[^] represents probability of observed result using chi-squared test of independence.

[&]amp; represents probability of observed result using Wilcoxon Rank-Sum test.

^{*} denominators do not include the 131 women (106 pregnant and 25 not pregnant) who did not return after the enrollment visit.





⁸ pregnant patients not initiated on ART were started on the following prophylactic regimens: from 2007-2009, single-dose niverapine + AZT/3TC until 7 days postpartum; from 2010-2013, zidovudine starting as early as 14 weeks gestation

Fig 1. Flow chart describing study population.

https://doi.org/10.1371/journal.pone.0195231.g001

5.8), and cumulative proportions of pregnant and non-pregnant patients lost to care at 1, 2, 3, 4 and 5 years after enrollment were as follows: for pregnant patients, 23.1% (95% CI 20.9–25.4%), 32.3% (95% CI 29.9–35.0%), 37.9% (95% CI 35.3–40.7%), 41.8% (95% CI 39.1–44.6%), and 46.5% (95% CI 43.5–49.7%); for non-pregnant patients, 19.2% (95% CI 16.3–22.5%), 28.5% (95% CI 25.1–32.3%), 36.3% (95% CI 32.5–40.4%), 41.1% (95% CI 37.1–45.4%), and 46.7% (95% CI 42.4–51.2%), respectively. In bivariate analysis, loss to care did not differ significantly

^{*} Some patients who were not eligible for ART by CD4 count or World Health Organization stage criteria initiated ART within 3 months of enrollment



Table 2. Associations of demographic and clinical characteristics at enrollment and having no follow-up* after enrollment (N = 2175).

Characteristic	No follow-up * (n = 131)	Followed-up* (n = 2044)	Crude OR (95% CI)	Adjusted OR (95% CI)
Pregnant				
No	25 (3.7)	653 (96.3)	Ref.	Ref.
Yes	106 (7.1)	1391 (92.9)	1.99 (1.27, 3.11)	2.01 (1.24, 3.24)
Age (years)				
15-24	36 (9.7)	336 (90.3)	Ref.	Ref.
25-34	76 (5.8)	1225 (94.2)	0.58 (0.38, 0.88)	0.65 (0.42, 1.01)
35-45	19 (3.8)	483 (96.2)	0.37 (0.21, 0.65)	0.45 (0.25, 0.83)
CD4 count (cells/mm ³)				
< 200	13 (2.9)	433 (97.1)	Ref.	Ref.
200-350	23 (4.3)	516 (95.7)	1.48 (0.74, 2.97)	1.32 (0.65, 2.67)
> 350	62 (6.1)	958 (93.9)	2.16 (1.17, 3.96)	1.89 (1.01, 3.53)
Missing	33 (19.4)	137 (80.6)	8.02 (4.11, 15.70)	7.62 (3.83, 15.20)
WHO clinical stage				
I	87 (6.3)	1302 (93.7)	Ref.	Ref.
II	26 (5.7)	433 (94.3)	0.90 (0.57, 1.41)	1.00 (0.63, 1.60)
III	9 (3.6)	243 (96.4)	0.55 (0.28, 1.12)	0.85 (0.41, 1.76)
IV	3 (5.0)	57 (95.0)	0.79 (0.24, 2.57)	0.81 (0.24, 2.77)
Missing	6 (40.0)	9 (60.0)	9.98 (3.47, 28.70)	7.84 (2.52, 24.40)
Year of enrollment				
2007-2009	64 (6.5)	918 (93.5)	Ref.	Ref.
2010-2013	67 (5.6)	1126 (94.4)	0.85 (0.60, 1.22)	0.93 (0.64, 1.34)

OR = odds ratio.

CI = confidence interval.

WHO = World Health Organization.

Ref = referent category.

https://doi.org/10.1371/journal.pone.0195231.t002

between pregnant and non-pregnant women (HR 1.04, 95% CI 0.90–1.20; p = 0.6 for log-rank test). When adjusted for baseline characteristics and starting ART within three months after enrollment, hazards of loss to care remained similar for the two groups (adjusted HR for pregnant women versus non-pregnant women 1.08, 95% CI 0.93–1.26) (Table 3). Sensitivity analyses using a 182-day definition for loss to care demonstrated similar results for the entire follow-up period (aHR 1.09, 95% CI 0.95–1.25) as well as when follow-up time was limited to 24 months after enrollment (aHR 1.19, 95% CI 0.99–1.43).

Discussion

This analysis of loss to HIV care of Congolese women found that those pregnant at care enrollment were more likely to never return for follow-up. However, among those who attended at least one follow-up visit, there were no statistically significant differences in loss to care by enrollment pregnancy status. This suggests that further efforts to retain women diagnosed with HIV in pregnancy should focus at the earliest point in care delivery, and that once pregnant women are established in care they can be retained in care as well as non-pregnant women.

About 6% of women who enrolled into care never returned for a follow-up visit. This was about twice as likely to occur among pregnant women versus non-pregnant women. Our

^{*} Patients were classified as having no follow-up if they did not return to care after the initial enrollment visit and otherwise were classified as followed-up.



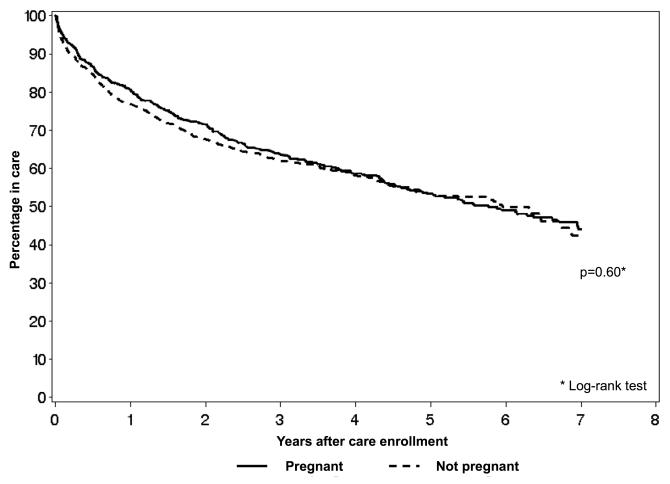


Fig 2. Kaplan-Meier curves for time to loss to care among those who returned for at least one post-enrollment visit, by pregnancy status at enrollment (N = 2044). Includes participants who had ≥ 1 follow-up visit after enrollment. Pregnancy status was recorded at enrollment into care. Participants were classified as lost to care (on their last clinic visit) if > 365 days had passed since their last clinic visit. All participants who did not experience the outcome were censored at the date of last clinic visit or when they were no longer at risk for loss to care (365 days before the database closing date).

https://doi.org/10.1371/journal.pone.0195231.g002

results are similar to other studies undertaken both prior to and after implementation of Option B+, which found that pregnant women are two to five times more likely to never return after enrollment into care [11–13, 27]. Many women diagnosed with HIV during routine prenatal screening may be overwhelmed by needing to simultaneously process their diagnosis and deal with competing demands of pregnancy [28–30]. Notably, the proportion of women who never returned for a follow-up visit in our study was substantially lower than these other cohorts [11–13, 27], where 20–33% of patients did not return after the enrollment visit. This finding may be due to the fact that most women in our study were referred to the HIV care and treatment sites from affiliated clinics. It is possible that a substantial proportion of HIV infected women referred to those clinics were lost to care prior to the enrollment visit by never acting on the referral.

Among women who attended at least one follow-up visit, we found no difference in the hazards of loss to care between pregnant and non-pregnant women, before and after adjusting for baseline differences between these groups. This result differs somewhat from those reported by Haas, et al [12]. In that study, among pregnant and non-pregnant women attending at least one follow-up visit after enrollment, pregnant women had lower odds of retention at years 1 and 2 after enrollment versus non-pregnant women, a difference that was no longer



Table 3. Associations of demographic and clinical characteristics at enrollment and loss to care among HIV-infected women with at least one visit after enrollment in care (N = 2044).

Characteristic	Lost to care (n = 860)	Not lost to care (n = 1184)	Crude HR* (95% CI)	* Adjusted HR (95% CI)
Pregnant				
No	288 (44.1)	365 (55.9)	Ref.	Ref.
Yes	572 (41.1)	819 (58.9)	1.04 (0.90, 1.20)	1.08 (0.93, 1.26)
Age (years)				
15–24	176 (52.4)	160 (47.6)	Ref.	Ref.
25–34	521 (42.5)	704 (57.5)	0.72 (0.60, 0.85)	0.76 (0.64, 0.90)
35–45	163 (33.8)	320 (66.3)	0.52 (0.42, 0.65)	0.57 (0.46, 0.71)
CD4 count (cells/mm³)				
< 200	145 (33.5)	288 (66.5)	Ref.	Ref.
200-350	194 (37.6)	322 (62.4)	1.10 (0.89, 1.36)	1.08 (0.87, 1.34)
> 350	446 (46.6)	512 (53.4)	1.39 (1.15, 1.67)	1.31 (1.08, 1.58)
Missing	75 (54.8)	62 (45.3)	1.99 (1.50, 2.63)	2.05 (1.54, 2.72)
WHO clinical stage				
I	574 (44.1)	728 (55.9)	Ref.	Ref.
II	176 (40.7)	257 (59.4)	0.89 (0.75, 1.05)	0.99 (0.83, 1.17)
III	86 (35.4)	157 (64.6)	0.77 (0.61, 0.97)	0.88 (0.70, 1.12)
IV	18 (31.6)	39 (68.4)	0.73 (0.45, 1.16)	0.76 (0.47, 1.22)
Missing	6 (66.7)	3 (33.3)	1.78 (0.80, 3.98)	1.32 (0.58, 2.99)
Year of enrollment				
2007–2009	376 (41.0)	542 (59.0)	Ref.	Ref.
2010–2013	484 (43.0)	642 (57.0)	1.52 (1.32, 1.75)	1.56 (1.35, 1.80)
ART initiated within 3 months				
No	607 (48.8)	637 (51.2)	Ref.	Ref.
Yes	253 (31.6)	547 (68.4)	0.60 (0.52, 0.69)	0.54 (0.44, 0.65)

HR = hazard ratio.

CI = confidence interval.

WHO = World Health Organization.

ART = antiretroviral therapy.

Ref = referent category.

Includes participants who had ≥ 1 follow-up visit after enrollment. Pregnancy status was recorded at enrollment into care. Participants were classified as lost to care (on their last clinic visit) if > 365 days had passed since their last clinic visit. All participants who did not experience the outcome were censored at the date of last clinic visit or when they were no longer at risk for loss to care (365 days before the database closing date).

https://doi.org/10.1371/journal.pone.0195231.t003

significant at year 3 of follow-up. The study by Haas, et al compared pregnant women on Option B+ (immediate ART initiation) to non-pregnant women initiating ART because they met immunological criteria. It is possible that the stronger negative effect of pregnancy on retention they reported resulted from differences between pregnant and non-pregnant women with respect to time in care prior to ART initiation: pregnant women were eligible for immediate ART initiation, whereas women initiating ART because of meeting immunological criteria typically needed to be in care at least long enough to be evaluated for ART eligibility. Other studies that did not distinguish between patients with no follow-up and those who attended at least one follow-up visit have also reported higher loss to follow-up among pregnant women initiating ART compared to non-pregnant women [31–33]. Similar to the Haas et al. study, in these studies, follow-up for non-pregnant women started at ART initiation, inducing a left-

^{*} HRs calculated from proportional hazards models of time to last clinic visit.



censoring bias (any loss to follow-up that occurred between enrollment and ART initiation was not included in the analyses). Our analysis attempts to control for this bias by counting follow-up time in both groups from enrollment and is more relevant to the current context of test-and-treat in which all HIV-infected patients are expected to start ART immediately.

While few studies have described long-term loss to care of pregnant women in HIV care, Haas et al. reported that over 30% of pregnant women were lost at three years after enrollment [12]. Similarly, in our study, we observed that loss to care was high for both pregnant and nonpregnant women, with nearly half the cohort lost to follow-up at five years after enrollment. We further observed that older age, more advanced HIV, and starting ART within three months of enrollment were associated with a lower hazard of loss to follow-up, consistent with findings from other studies [34-36]. Feeling healthy, stigma and anxiety about lifelong treatment are established barriers to retention in HIV care, and may explain these results [37, 38]. Among women enrolling in HIV care while pregnant, specific barriers to retention include prioritizing children's health over their own, non-disclosure to partners, HIV status denial, and economic concerns [39-41]. While few other studies have examined long-term retention in care of pregnant women, attrition of 30-50% of patients initiating care has been observed in cohorts of general populations [42, 43], adolescents [44], and special populations in sub-Saharan Africa [45]. Although our results reflect the challenges of maintaining patients in longterm HIV care, our finding that patients who initiated ART within 3 months of care enrollment were nearly twice as likely to remain in care as those who did not suggests that early ART initiation under universal test and treat may promote greater retention in care than observed to date in sub-Saharan Africa.

This study has several limitations. The cohort consisted of patients from only two clinics in a country with a relatively low prevalence and burden of HIV compared to other sub-Saharan African countries, which may limit the generalizability of our findings. Additionally, we only included women who enrolled in care in these clinics, but were unable to account for women who were referred to the clinics and never enrolled. While some patients were known to have died or transferred to other facilities, it is possible that additional patients unknowingly experienced these outcomes and were misclassified as lost to care. Because we analyzed previously collected data, we were unable to examine additional factors (e.g., income, distance from clinic) that may have influenced outcomes.

Conclusions

In this large cohort of women enrolled in HIV care in two clinics in Kinshasa, DRC, we found similar rates of loss to care among pregnant and non-pregnant women. These results suggest that pregnancy itself may not be the main driver of poor retention in HIV care but that confounding factors may also be responsible for the high attrition noted during the early implementation of universal treatment of pregnant women living with HIV under Option B+. As universal test and treat is implemented across sub-Saharan Africa, special attention should be paid to the problem of drop-out immediately following enrollment.

Acknowledgments

The authors thank the patients at participating sites as well as the clinical staff who collected the data used in this analysis.

Author Contributions

Conceptualization: Jonathan Ross, Andrew Edmonds, Donald R. Hoover, Qiuhu Shi, Kathryn Anastos, Marcel Yotebieng.



Data curation: Andrew Edmonds, Qiuhu Shi, Marcel Yotebieng.

Formal analysis: Jonathan Ross, Andrew Edmonds, Donald R. Hoover, Qiuhu Shi, Kathryn Anastos, Marcel Yotebieng.

Funding acquisition: Jonathan Ross, Kathryn Anastos, Marcel Yotebieng.

Investigation: Andrew Edmonds, Patricia Lelo, Frieda Behets, Marcel Yotebieng.

Methodology: Jonathan Ross, Andrew Edmonds, Donald R. Hoover, Qiuhu Shi, Kathryn Anastos, Marcel Yotebieng.

Project administration: Jonathan Ross, Kathryn Anastos, Patricia Lelo, Frieda Behets, Marcel Yotebieng.

Resources: Qiuhu Shi, Patricia Lelo, Frieda Behets, Marcel Yotebieng.

Software: Andrew Edmonds, Donald R. Hoover, Qiuhu Shi.

Supervision: Kathryn Anastos, Frieda Behets, Marcel Yotebieng.

Validation: Jonathan Ross, Andrew Edmonds, Donald R. Hoover, Qiuhu Shi, Kathryn Anastos, Frieda Behets, Marcel Yotebieng.

Visualization: Jonathan Ross, Andrew Edmonds, Qiuhu Shi.

Writing - original draft: Jonathan Ross.

Writing – review & editing: Jonathan Ross, Andrew Edmonds, Donald R. Hoover, Qiuhu Shi, Kathryn Anastos, Patricia Lelo, Frieda Behets, Marcel Yotebieng.

References

- AIDSInfo 2015. Geneva: Joint UN Programme on HIV/AIDS, 2017. Available from: http://aidsinfo.unaids.org. Cited 20 June 2017.
- Countdown to zero: Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Geneva: Joint UN Programme on HIV/AIDS; 2011. Available from: http://www.unaids.org/sites/default/files/media_asset/20110609_JC2137_Global-Plan-Elimination-HIV-Children_en_1.pdf. Cited 20 June 2017.
- De Cock KM, Fowler MG, Mercier E, de Vincenzi I, Saba J, Hoff E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. JAMA. 2000; 283(9):1175–82. PMID: 10703780
- Sturt AS, Dokubo EK, Sint TT. Antiretroviral therapy (ART) for treating HIV infection in ART-eligible pregnant women. Cochrane Database Syst Rev. 2010(3):CD008440. https://doi.org/10.1002/14651858.CD008440 PMID: 20238370
- Fowler MG, Qin M, Fiscus SA, Currier JS, Flynn PM, Chipato T, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. New Engl J Med. 2016; 375(18):1726–37. https://doi.org/10.1056/NEJMoa1511691 PMID: 27806243
- 6. On the fast-track to an AIDS-free generation: the incredible journey of the Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive. Geneva: Joint UN Programme on HIV/AIDS, 2016. Available from: http://www.unaids.org/sites/default/files/media_asset/GlobalPlan2016_en.pdf. Cited 20 June 2017.
- 7. Clouse K, Pettifor A, Shearer K, Maskew M, Bassett J, Larson B, et al. Loss to follow-up before and after delivery among women testing HIV positive during pregnancy in Johannesburg, South Africa. Tropical Med Int Health. 2013; 18(4):451–60.
- Rawizza HE, Chang CA, Chaplin B, Ahmed IA, Meloni ST, Oyebode T, et al. Loss to Follow-Up within the Prevention of Mother-to-Child Transmission Care Cascade in a Large ART Program in Nigeria. Curr HIV Res. 2015; 13(3):201–9. PMID: 25986371
- Phillips T, Thebus E, Bekker LG, McIntyre J, Abrams EJ, Myer L. Disengagement of HIV-positive pregnant and postpartum women from antiretroviral therapy services: a cohort study. J Int AIDS Soc. 2014; 17:19242. https://doi.org/10.7448/IAS.17.1.19242 PMID: 25301494



- Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach. WHO Guidelines Approved by the Guidelines Review Committee. Geneva, 2013. Available from: http://apps.who.int/iris/bitstream/10665/85321/1/ 9789241505727_eng.pdf. Cited 20 June 2017.
- Llenas-Garcia J, Wikman-Jorgensen P, Hobbins M, Mussa MA, Ehmer J, Keiser O, et al. Retention in care of HIV-infected pregnant and lactating women starting ART under Option B+ in rural Mozambique. Trop Med Int Health. 2016; 21(8):1003–12. https://doi.org/10.1111/tmi.12728 PMID: 27208807
- 12. Haas AD, Tenthani L, Msukwa MT, Tal K, Jahn A, Gadabu OJ, et al. Retention in care during the first 3 years of antiretroviral therapy for women in Malawi's option B+ programme: an observational cohort study. Lancet HIV. 2016; 3(4):e175–82. https://doi.org/10.1016/S2352-3018(16)00008-4 PMID: 27036993
- 13. Tenthani L, Haas AD, Tweya H, Jahn A, van Oosterhout JJ, Chimbwandira F, et al. Retention in care under universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ('Option B+') in Malawi. AIDS. 2014; 28(4):589–98. https://doi.org/10.1097/QAD.000000000000143 PMID: 24468999
- Landes M, Sodhi S, Matengeni A, Meaney C, van Lettow M, Chan AK, et al. Characteristics and outcomes of women initiating ART during pregnancy versus breastfeeding in Option B+ in Malawi. BMC Public Health. 2016; 15:713. https://doi.org/10.1186/s12889-016-3380-7 PMID: 27487775
- 15. Pati R, Lahuerta M, Elul B, Okamura M, Alvim MF, Schackman B, et al. Factors associated with loss to clinic among HIV patients not yet known to be eligible for antiretroviral therapy (ART) in Mozambique. J Int AIDS Soc. 2013; 16:18490. https://doi.org/10.7448/IAS.16.1.18490 PMID: 23755857
- Grimsrud A, Cornell M, Schomaker M, Fox MP, Orrell C, Prozesky H, et al. CD4 count at antiretroviral therapy initiation and the risk of loss to follow-up: results from a multicentre cohort study. J Epidemiol Community Health. 2016; 70(6):549–55. https://doi.org/10.1136/jech-2015-206629 PMID: 26700300
- 17. Dzangare J, Takarinda KC, Harries AD, Tayler-Smith K, Mhangara M, Apollo TM, et al. HIV testing uptake and retention in care of HIV-infected pregnant and breastfeeding women initiated on 'Option B+' in rural Zimbabwe. Tropical Med Int Health. 2016; 21(2):202–9.
- Edmonds A, Lusiama J, Napravnik S, Kitetele F, Van Rie A, Behets F. Anti-retroviral therapy reduces incident tuberculosis in HIV-infected children. Int J Epidemiol. 2009; 38(6):1612–21. https://doi.org/10. 1093/ije/dyp208 PMID: 19448046
- Edmonds A, Yotebieng M, Lusiama J, Matumona Y, Kitetele F, Napravnik S, et al. The effect of highly active antiretroviral therapy on the survival of HIV-infected children in a resource-deprived setting: a cohort study. PLoS Med. 2011; 8(6):e1001044. https://doi.org/10.1371/journal.pmed.1001044 PMID: 21695087
- Global Plan Country Fact Sheet—Democratic Republic of Congo, 2016. Geneva: Joint UN Programme on HIV/AIDS, 2016. Available from: http://www.unaids.org/sites/default/files/media/documents/ UNAIDS GlobalplanCountryfactsheet drc en.pdf. Cited 20 June 2017.
- 21. Ministère du Plan et Suivi de la Mise en œuvre de la Révolution de la Modernité et Ministère de la Santé Publique, République Démocratique du Congo 2013–1014: Rapport Préliminaire sur la Prévalence du VIH. Calverton, Maryland, U.S.A: Ministère du Plan et Macro International; 2014. Available from: https://dhsprogram.com/pubs/pdf/FR300/FR300.pdf. Cited 20 June 2017.
- Yotebieng M, Chalachala JL, Labbok M, Behets F. Infant feeding practices and determinants of poor breastfeeding behavior in Kinshasa, Democratic Republic of Congo: a descriptive study. Int Breastfeed J. 2013; 8(1):11. https://doi.org/10.1186/1746-4358-8-11 PMID: 24083882
- 23. Yotebieng M, Labbok M, Soesters H, Chalachala JL, Lapika B, Vitta B, et al. Ten Steps to Successful Breastfeeding programme to promote early initiation and exclusive breastfeeding in DR Congo: a cluster-randomised controlled trial. Lancet Glob Health. 2015; 2015 Sep; 3(9):e546–55. https://doi.org/10.1016/S2214-109X(15)00012-1 PMID: 26246225
- 24. World Health Organization. Antiretroviral drugs for treating pregnant women and prevention HIV infection in infants: guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings. Geneva, Switzerland, 2004. Available from: http://www.who.int/hiv/pub/mtct/en/arvdrugswomenguidelinesfinal.pdf?ua=1. Cited 20 June 2017.
- 25. World Health Organization. Antiretroviral drugs for treating pregnant women and prevention HIV infection in infants: recommendations for a public health approach. Geneva, Switzerland, 2006. Available from: http://www.who.int/pub/mtct/antiretroviral/en/. Cited 20 June 2017.
- 26. World Health Organization. Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access—2010 version. Geneva, Switzerland, 2010. Available from: http://www.who.int/hiv/pub/mtct/antiretroviral2010/en/index.html. Cited 20 June 2017.
- Schnippel K, Mongwenyana C, Long LC, Larson BA. Delays, interruptions, and losses from prevention
 of mother-to-child transmission of HIV services during antenatal care in Johannesburg, South Africa: a
 cohort analysis. BMC Infect Dis. 2015; 15:46. https://doi.org/10.1186/s12879-015-0778-2 PMID:
 25656597



- Stinson K, Myer L. Barriers to initiating antiretroviral therapy during pregnancy: a qualitative study of women attending services in Cape Town, South Africa. Afr J AIDS Res. 2012; 11(1):65–73. https://doi. org/10.2989/16085906.2012.671263 PMID: 25870899
- Yotebieng M, Thirumurthy H, Moracco KE, Kawende B, Chalachala JL, Wenzi LK, et al. Conditional
 cash transfers and uptake of and retention in prevention of mother-to-child HIV transmission care: a randomised controlled trial. Lancet HIV. 2016; 3(2):e85–93. https://doi.org/10.1016/S2352-3018(15)
 00247-7 PMID: 26847230
- 30. Yotebieng M, Moracco KE, Thirumurthy H, Edmonds A, Tabala M, Kawende B, et al. Conditional cash transfers improve retention in PMTCT services by mitigating the effect of not having money to come to the clinic. Journal Acquir Immune Defic Syndr. 2017; 74(2): 150–157.
- Kaplan R, Orrell C, Zwane E, Bekker LG, Wood R. Loss to follow-up and mortality among pregnant women referred to a community clinic for antiretroviral treatment. AIDS. 2008; 22(13):1679–81. https://doi.org/10.1097/QAD.0b013e32830ebcee PMID: 18670232
- Boyles TH, Wilkinson LS, Leisegang R, Maartens G. Factors influencing retention in care after starting antiretroviral therapy in a rural South African programme. PLoS One. 2011; 6(5):e19201. https://doi. org/10.1371/journal.pone.0019201 PMID: 21559280
- Wang B, Losina E, Stark R, Munro A, Walensky RP, Wilke M, et al. Loss to follow-up in a community clinic in South Africa—roles of gender, pregnancy and CD4 count. S Afr Med J. 2011; 101(4):253–7. PMID: 21786730
- Mitiku I, Arefayne M, Mesfin Y, Gizaw M. Factors associated with loss to follow-up among women in Option B+ PMTCT programme in northeast Ethiopia: a retrospective cohort study. J Int AIDS Soc. 2016; 19(1):20662. https://doi.org/10.7448/IAS.19.1.20662 PMID: 27005750
- 35. Gwynn RC, Fawzy A, Viho I, Wu Y, Abrams EJ, Nash D. Risk factors for loss to follow-up prior to ART initiation among patients enrolling in HIV care with CD4+ cell count >/ = 200 cells/muL in the multi-country MTCT-Plus Initiative. BMC Health Serv Res. 2015; 15:247. https://doi.org/10.1186/s12913-015-0898-9 PMID: 26108273
- Clouse K, Pettifor AE, Maskey M, Bassett J, Van Rie A, Behets F, et al. Patient retention from HIV diagnosis through one year on antiretroviral therapy at a primary healthcare clinic in Johannesburg, South Africa. J Acquir Immune Defic Syndr. 2013; 62(2): e39–e49. https://doi.org/10.1097/QAI. 0b013e318273ac48 PMID: 23011400
- 37. Kim MH, Zhou A, Mazenga A, Ahmed S, Markham C, Zomba G, Simon K, et al. Why did I stop? Barriers and facilitators to uptake and adherence to ART in Option B+ HIV Care in Lilongwe, Malawi. PLoS One; 11(2):e0149527. https://doi.org/10.1371/journal.pone.0149527 PMID: 26901563
- 38. Layer EH, Kennedy CE, Beckham SW, Mbwambo JK, Likindikoki S, Davis WW, et al. Multi-level factors affecting entry into and engagement in the HIV continuum of care in Iringa, Tanzania. PLoS One. 2014; 9(8):e104961. https://doi.org/10.1371/journal.pone.0104961 PMID: 25119665
- Clouse K, Schwartz S., Van Rie A., Bassett J, Yende N, Pettifor A. "What they wanted was to give birth; nothing else": barriers to retention in option B+ HIV care among postpartum women in South Africa. J Acquir Immune Defic Syndr. 2014; 67(1):e12–8. https://doi.org/10.1097/QAI.0000000000000263 PMID: 24977376
- 40. Tweya H, Gugsa S, Hosseinipour M, Speight C, Ng'ambi W, Bokosi M, et al. Understanding factors, outcomes and reasons for loss to follow-up among women in Option B+ PMTCT programme in Lilongwe, Malawi. Trop Med Int Health. 2014; 19(11):1360–6. https://doi.org/10.1111/tmi.12369 PMID: 25087778
- Duff P, Kipp W, Wild TC, Rubaale T, Okech-Ojony J. Barriers to accessing highly active antiretroviral therapy by HIV-positive women attending an antenatal clinic in a regional hospital in western Uganda. J Int AIDS Soc. 2010; 13:37. https://doi.org/10.1186/1758-2652-13-37 PMID: 20863399
- 42. Mutasa-Apollo T, Shiraishi RW, Takarinda KC, Dzangare J, Mugurungi O, Murungu J, et al. Patient retention, clinical outcomes and attrition-associated factors of HIV-infected patients enrolled in Zimbabwe's National Antiretroviral Therapy Programme, 2007–2010. PLoS One. 2014; 9(1):e86305. https://doi.org/10.1371/journal.pone.0086305 PMID: 24489714
- 43. Koole O, Tsui S, Wabwire-Mangen F, Kwesigabo G, Menten J, Mulenga M, et al. Retention and risk factors for attrition among adults in antiretroviral treatment programmes in Tanzania, Uganda and Zambia. Tropical Med Int Health. 2014; 19(12):1397–410.
- Okoboi S, Ssali L, Yansaneh Al, Bakanda C, Birungi J, Nantume S, et al. Factors associated with longterm antiretroviral therapy attrition among adolescents in rural Uganda: a retrospective study. J Int AIDS Soc. 2016; 19(5 Suppl 4):20841.
- 45. Vuylsteke B, Semde G, Auld AF, Sabatier J, Kouakou J, Ettiegne-Traore V, et al. Retention and risk factors for loss to follow-up of female and male sex workers on antiretroviral treatment in Ivory Coast: a retrospective cohort analysis. J Acquir Immune Defic Syndr. 2015; 68 Suppl 2:S99–S106.