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Journal

JAIDS Journal of Acquired Immune Deficiency Syndromes, 74(3)

ISSN

1525-4135

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Publication Date

2017-03-01

DOI

10.1097/qai.0000000000001228

Peer reviewed

Published in final edited form as:

J Acquir Immune Defic Syndr. 2017 March 01; 74(3): 279–284. doi:10.1097/QAI.0000000000001228.

Viral Suppression and Retention in Care up to 5 Years after Initiation of Lifelong ART during Pregnancy (Option B+) in Rural Uganda

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Abstract

Background—Lifelong antiretroviral therapy (ART) is recommended for all HIV-infected pregnant women, but early studies suggest women often drop out of care postpartum and data are limited on virologic outcomes.

Methods—We evaluated viral suppression (primary outcome) and retention in care up to 5 years after ART initiation among HIV-infected women who started lifelong ART during pregnancy, irrespective of CD4 count, in a study in rural Uganda (NCT00993031). Participants were followed in the study for up to 1 year postpartum, then referred to clinics in surrounding communities. A random sample (N=200) was invited to participate in a cross-sectional follow-up study after completing the trial, involving one visit for a questionnaire and pregnancy and HIV RNA testing. Retention in care was defined as having attended an HIV clinic in the last 90 days. Logistic regression models were used to examine factors associated with viral suppression (HIV-1 RNA ≤400 copies/ml) at follow-up.

Results—One hundred fifty women (75%) were successfully contacted for follow-up at a median of 4.2 years after starting ART; 135 were retained in care (90%, 95% CI 84.0%–94.3%) and 121 demonstrated viral suppression (80.7%, 95% CI 73.4% –86.7%). Women who had disclosed their

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Prior presentation: These data were presented at the Conference on Retroviruses and Opportunistic Infections, February 24, 2016, Boston, MA (Abstract 796).

Conflicts of interest: Gilead donates medications for participants in a separate NIH-funded study led by D.V.H. but provides no financial support. All other authors declare no competing interests.

HIV status to their primary partner had greater odds of viral suppression (aOR 4.51, 95% CI 1.02–19.8).

Conclusions—High rates of viral suppression can be achieved up to 5 years after initiating ART during pregnancy among women retained in care. Interventions to facilitate disclosure may improve long-term outcomes among women who initiate ART during pregnancy under universal treatment.

Keywords

Antiretroviral therapy; breastfeeding; loss to follow-up; Option B+; pregnancy; viral load

INTRODUCTION

In 2013, the World Health Organization (WHO) issued guidelines recommending Option B+, or the provision of combination antiretroviral therapy (ART) to all pregnant and breastfeeding HIV-infected women, regardless of CD4 cell count, to be continued for life.[1] This strategy has several benefits, including prevention of HIV transmission during pregnancy and breastfeeding, reduction in the risk of sexual transmission, and preservation of a woman's health through uninterrupted use of ART. However, in order to fully realize the promise of Option B+, and now universal treatment,[2] women must remain in care and maintain virologic suppression well beyond the initial period of pregnancy and breastfeeding.

Although there have been significant gains in the number of HIV-infected women initiating ART during pregnancy worldwide,[3] concerns have been raised across sub-Saharan Africa about the implementation of Option B+ and about attrition along the cascade of care. In Malawi, which pioneered Option B+ in 2011,[4] only two-thirds of women starting ART during pregnancy are retained in care at 3 years,[5] and loss to follow-up among women initiated on Option B+ is higher than among women initiating ART for other clinical indications, such as low CD4 cell count or advanced WHO stage.[5, 6] To date, little is known outside of Malawi about longer-term retention in care several years after the cessation of breastfeeding. Moreover, despite the critical importance of viral suppression for successful treatment, data also remain limited on virologic outcomes among women initiated on Option B+, particularly in rural sites and beyond one year postpartum.

Uganda adopted Option B+ in 2012[7] with roll-out to clinics throughout the country during 2013. Data collected by weekly SMS reporting from over 1600 Ministry of Health facilities indicate that more than 95% of pregnant women are tested for HIV and that most HIV-infected pregnant women are initiated on ART.[8] As in much of southern and eastern Africa, in Uganda, data are limited on outcomes following pregnancy, particularly regarding retention in care and rates of viral suppression. To address these knowledge gaps, we sought to evaluate viral suppression and retention in care up to 5 years after the initiation of lifelong ART during pregnancy in a population of previously ART-naïve, HIV-infected women in rural Uganda originally participating in a clinical trial of HIV and malaria.

METHODS

Study Design and Population

We conducted a cross-sectional study, consisting of a single follow-up assessment, of previously ART-naïve, HIV-infected women who had initiated lifelong ART during pregnancy at 12–28 weeks gestation, regardless of CD4 cell count, in the PROMOTE-Pregnant Women and Infants (PROMOTE-PIs) study (ClinicalTrials.gov, NCT00993031).[9–14] PROMOTE-PIs was a randomized trial designed to test the hypothesis that lopinavir compared to efavirenz would reduce the prevalence of placental malaria. The primary study endpoint, placental malaria, did not differ between the study arms.[14] Viral suppression at delivery was higher among women on efavirenz (97.6%) than lopinavir (86%).[9] The study site was in Tororo, a district in rural eastern Uganda with an HIV prevalence of approximately 7% among antenatal clinic attendees at the district hospital.[15] The study was conducted from December 2009 to March 2013 and enrolled 389 women at a median of 21 weeks gestation and median CD4 cell count 370 cells/mm^3. Study participants initiated lifelong ART up to 3 years before the Uganda Ministry of Health adopted Option B + as part of national guidelines.[7] Participants breastfed their infants and were followed in the study for up to 1 year postpartum, then were referred to clinics in the surrounding communities to continue ART. HIV care was provided at the clinics according to Uganda Ministry of Health Guidelines without viral load monitoring.

Study Procedures and Measurements

Of 389 women enrolled in PROMOTE-PIs, a random sample of 200 women was invited to participate in a cross-sectional follow-up study (PROMOTE B+) after completing the trial (Figure 1). Home visitors made up to 3 contact attempts to locate the participant, either by phone or in person, to provide an invitation to participate in the study. If the participant could not be located, the home visitor attempted to obtain information on vital status and whether the participant had relocated. For those who were successfully contacted for follow-up (located and consented), a single study visit was conducted at our study clinic in Tororo. A questionnaire was administered to assess demographics, food insecurity (operationalized by the Household Hunger Scale[16]), partnerships, and subsequent pregnancies. The date of the most recent HIV clinic visit, ART regimen, and CD4 cell count were abstracted from provider documentation in participants' personal clinical record booklets. Participants who were not already known to be pregnant underwent urine pregnancy testing. HIV-1 RNA testing was performed for all participants using the COBAS AmpliPrep/COBAS TaqMan HIV-1 test, version 2.0 (Roche Molecular Diagnostics, Pleasanton, California, USA).

The study protocol was approved by the Makerere University School of Medicine Research and Ethics Committee, the Uganda National Council of Science and Technology, and the University of California, San Francisco Committee on Human Research. All participants provided written informed consent in their preferred language.

Outcomes and Statistical Analysis

The primary outcome for this analysis was viral suppression (HIV-1 RNA ≤400 copies/ml) at the follow-up visit. Retention in care, the secondary outcome, was defined as having

attended an HIV clinic in the preceding 90 days. We selected this definition based on the usual interval between visits at clinics in Tororo district (30 to 60 days). Logistic regression models were used to examine factors associated with viral suppression. Predictors were included in multivariate models based on our causal model for viral suppression, with final models chosen by backward stepwise selection. We conducted a sensitivity analysis in which women who were not successfully contacted for follow-up in this study were assigned to a status of out of care and virologic non-suppression. Statistical analyses were performed using Stata software version 13 (College Station, Texas, USA).

RESULTS

Characteristics of Study Participants

From March to September 2015, of 200 randomly selected women, 150 (75%) were successfully contacted for follow-up and presented to the study clinic for evaluation (Figure 1). Of the 50 women who were not successfully contacted, 38 could not be located, 2 were deceased, 7 were not interested in the study, and 3 reported being interested in the study but did not present to the clinic for evaluation. Baseline characteristics were similar between women who were enrolled and not enrolled in PROMOTE B+, including age (34.3 vs. 31.9 years), phone ownership (46% vs. 50%), and initial treatment arm (52% vs. 60% on efavirenz), except that more women who were not enrolled had been withdrawn from the PROMOTE-PIs study, at a median of 9 months postpartum, most commonly due to relocating.

The median age of the 150 enrolled participants was 34.5 years (interquartile range [IQR] 29.9–37.6), (Table 1). Participants were enrolled at a median of 4.2 years (range 2.7–5.3; IQR 3.4–4.7) after ART initiation and the median number of years postpartum was 3.8 (range 2.2–5.0; IQR 3.1–4.3). A total of 131 participants (87.3%) were on ART (78 on efavirenz, 35 on nevirapine, and 18 on lopinavir-based regimens). Fifty-eight (38.7%) participants reported at least one subsequent pregnancy after initiating ART; at the time of follow-up, 19 (12.7%) were pregnant and 23 (15.3%) were breastfeeding. Participants were receiving care at a total of 33 clinics across Uganda, predominantly in Tororo district and in Kampala.

Retention in Care and Virologic Outcomes

Long-term retention in care following initiation of Option B+ was 90% (95% confidence interval [CI] 84.0% –94.3%), with 135 of 150 women having been seen for HIV care in the last 90 days (Table 2). Among the 150 participants enrolled, viral suppression was 80.7% (95% CI 73.4% –86.7%), and among the 135 participants who were retained in care, viral suppression was 89.6% (95% CI 83.2% –94.2%). In a sensitivity analysis, in which we assigned those who were not enrolled as being out of care (missing = failure), retention in care was 67.5% (95% CI 60.5% –73.9%). Assigning those who were not enrolled to a status of virologic non-suppression, viral suppression was 60.5% (95% CI 53.6% –67.3%). Stratifying by the number of years since ART initiation, a high proportion of participants maintained viral suppression across each time point (Figure 2). Using a higher threshold of

1000 copies/ml to define viral suppression, 3 additional participants met this criteria, for a total of 124 of the 150 enrolled participants (82.7%, 95% CI 75.6–88.4%).

In univariate analysis, factors associated with viral suppression included having disclosed one's HIV status to one's primary partner (odds ratio [OR] 5.24, 95% CI 1.21–22.6) and food security (OR 2.61, 95% CI 1.00–6.88), (Table 3). We did not find an association between viral suppression and current pregnancy or breastfeeding status (OR 0.98, 95% CI 0.40–2.44). In a multivariate model, disclosure of HIV status to one's primary partner remained significantly associated with greater odds of viral suppression (adjusted odds ratio [aOR] 4.51, 95% CI 1.02–19.8).

DISCUSSION

In this study, among women who were successfully contacted up to 5 years after the initiation of lifelong ART during pregnancy (Option B+), 90% were retained in care and 81% demonstrated HIV-1 RNA suppression. This level of viral suppression was achieved in the context of routine care under Uganda Ministry of Health Guidelines without viral load monitoring. Women who had disclosed their HIV status to their primary partner were over four times more likely to be virologically suppressed, and there was a trend toward higher odds of viral suppression among women who were food secure in multivariate analysis.

This is among the first studies to report on virologic outcomes beyond 1 year postpartum in a population that initiated lifelong ART during pregnancy irrespective of CD4 cell count. We found high levels of viral suppression (nearly 90%) among women retained in care. The limited existing data on virologic outcomes under Option B+ demonstrate a wide range of rates of viral suppression at delivery and up to 12 months postpartum, with further variation by practice setting and in the frequency of viral load monitoring. Moreover, studies have used different thresholds for viral suppression, making comparisons across studies somewhat challenging. A study of 88 women in Lesotho found that 69% of participants achieved viral suppression to <400 copies/ml at the critical time point of delivery.[17] In a study of over 1000 women starting Option B+ in public clinics in Malawi, 81% of women tested had HIV RNA <1000 copies/ml at 6 months after ART initiation, but 35% of women had no viral load testing performed. In a cohort of women who initiated ART during pregnancy in a study at a public clinic in Cape Town, South Africa in which viral loads were assessed routinely, 91% achieved viral suppression to <1000 copies/ml by delivery,[18] but only 70% maintained viral suppression to 12 month postpartum.[19]

Several studies in which pregnant women initiated ART based on CD4 count thresholds or that included women who initiated ART prior to or during pregnancy have raised some concerns about virologic outcomes in the postpartum period. For example, a study of women in Malawi who initiated ART at CD4 counts below 350 cells/mm^3 found detectable viremia (>50 copies/ml) in over one-quarter of women at 24 months postpartum.[20] A study in Soweto, South Africa that enrolled a cohort of pregnant women (median CD4 count 320 cells/mm^3), of whom 22% had initiated ART prior to pregnancy, found high rates of viral suppression (87%) to <400 copies/ml at delivery, but only 71% maintained viral suppression at 12 months postpartum.[21] In contrast, a cohort in western Uganda reported that women

who initiated ART for clinical indications (median CD4 count 165 cells/mm^3) were able to maintain high levels (>89%) of viral suppression to ≤400 copies/ml subsequently during pregnancy and up to 6 months postpartum.[22]

We found that disclosure of a participant's HIV status to her primary partner was associated with higher odds of long-term viral suppression. A recent study from Malawi also found that women who were retained in Option B+ programs were more likely than defaulters to have disclosed their HIV status to their primary partner and to be aware of their partner's HIV status.[23] Previous studies have demonstrated that male partner involvement is associated with improved uptake of services for the prevention of perinatal transmission[24] and HIV-free infant survival.[25, 26] Our results suggest that facilitated disclosure interventions may help women to maintain long-term treatment and viral suppression, particularly after delivery and the cessation of breastfeeding, when women remain in care for their own health.

Women who reported food security, based on access to sufficient quantities of food, were also more likely to achieve long-term viral suppression in our study in univariate analysis, with a trend in multivariate models. These results are consistent with our prior work demonstrating that food insufficiency is associated with a lack of sustained viral suppression during pregnancy and breastfeeding.[12] Previous studies of non-pregnant HIV-infected adults have reported poor virologic outcomes among food insecure individuals in the United States and Uganda.[27–30] Several studies have also evaluated interventions to address food security and improve clinic attendance and ART adherence,[31–33] although the optimal components of such strategies are not yet known. Our findings suggest that food insecurity may be an important and modifiable risk factor for successful long-term virologic outcomes for women well beyond the postpartum period.

Our results also demonstrate that retention in care may be sub-optimal among women who were not successfully contacted for follow-up. Although 90% of participants who enrolled in follow-up were found to be in care, if we assigned out of care status to the 50 women who were not successfully contacted, about one-third of women would be out of care. However, this approach likely misclassifies some patients who have transferred to other clinics as lost to follow-up. A tracking study of Option B+ patients in Malawi found that many patients thought to be lost to follow-up had transferred to other clinics.[34] Indeed, prior studies from adult ART clinics in Uganda that have employed sampling-based approaches and intensive tracking of patients lost to follow-up suggest that most of these patients are in care at other clinics.[35, 36] Therefore, it is likely that our sensitivity analysis resulted in underestimation of retention in care and viral suppression.

A potential benefit of Option B+ and universal, lifelong ART is that viral suppression may be achieved prior to or early in subsequent pregnancies, thereby reducing the risk of perinatal transmission. In settings such as Uganda, in which the fertility rate is 5.8 births per woman,[37] the ability to maintain viral suppression in subsequent pregnancies will be critical. One-third of participants in our study reported a subsequent pregnancy after ART initiation. Of the one-quarter who were pregnant or breastfeeding at the time of follow-up, it is reassuring that levels of viral suppression did not differ from women who were neither pregnant nor breastfeeding. High levels of viral suppression on entry into antenatal care

were also reported in a cohort of women in Cape Town, South Africa who had started ART prior to pregnancy.[38] However, additional data are needed in order to monitor and optimize outcomes during and between repeat pregnancies.

This study has several strengths, including the random selection of participants for follow-up. In addition, we were able to evaluate women who were receiving care at public and private clinics in Tororo District and across Uganda, limiting the biases that may result from evaluations of single health centers or health systems. A limitation of this study is that we were unable to successfully contact and enroll all 200 women randomly selected for follow-up. We attempted to address this in sensitivity analyses, in which we included the most conservative scenarios, assigning out of care status or virologic non-suppression to those participants who were not successfully enrolled for follow-up. However, as noted above, prior tracking studies suggest that many patients thought to be lost to follow-up have transferred to other clinics.[34–36] An additional limitation is that participants in our study had initiated Option B+ in the context of a clinical trial, in which viral load monitoring occurred and women may have received higher levels of support at the time of ART initiation than is routinely available. However, after 1 year postpartum, all participants were referred to local clinics for ongoing care under Ministry of Health guidelines without viral load monitoring for at least 2 years prior to this cross-sectional follow-up study.

In conclusion, our results demonstrate that successful viral suppression can be achieved among women retained in care up to 5 years after ART initiation during pregnancy, including in subsequent pregnancies. Interventions to facilitate disclosure and to address food insecurity may improve long-term outcomes among women who initiate lifelong ART during pregnancy. Given the challenges of tracking patient outcomes in our study and others, systems to allow for monitoring of patient outcomes across clinics may help to inform future estimates of long-term retention in care. With the scale-up of viral load monitoring in resource limited settings, further data are needed on virologic outcomes among women initiated on ART during pregnancy, a population for which successful treatment is critical to both maternal and child health.

Acknowledgments

The authors thank the participants for generously contributing their time to this study. We also thank the staff of the Infectious Diseases Research Collaboration, particularly Catherine Tugaineyo, Dr. Abel Kakuru, David Idewa, Joseph Okou, Moses Otweyo Okumu, Paul Oketch, Daniel Ochuli, Noeline Nalugo, David Otai, Frank Angiro, Tabitha Ayabo, Florence Nangobi, Saume Inacho, Jessy Oginero, Molly Adyero, Patience Nayebare, Charlie Ebusu, Cephus Ssemanda, Martin Okitwi, Harriet Ochokoru Adrama, Johnie Ategeka, Stephen Orena, Moses Were, Razack Wasswa, Robert Twine, Dickson Lyagoba, Lorna Aol, Julius Sejjemba, Nuru Marijan, Kate Imaira, Ambrose Turyashemererwa, Joseph Okoboi, David Ogwang, Raphael Odieno, Phoebe Amoile, Joseph Eyakina, Dr. Bridget Nzarubara, Faith Bagatya, Patience Aweko, Jacquiline Namyalo, Brian Omome, Sylvia Kamisha, Sarah Ruhukya, Hajarah Nansukusa, Bena Auma, Peggy Kakitojo, Hajara Kyokisa, and Mary Goretti.

Source of funding: This work was supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (K12 HD052163 [P.I. Brindis, Adler] to support C.A.K.), the National Institute of Allergy and Infectious Diseases (NIAID, T32 AI060530, D.V.H./C.A.K. and K24 AI051982, D.V.H.), and a Mentored Scientist Award (C.A.K.) from the University of California, San Francisco-Gladstone Institute of Virology & Immunology Center for AIDS Research through NIAID P30 AI027763 (P.I. Volberding, Greene). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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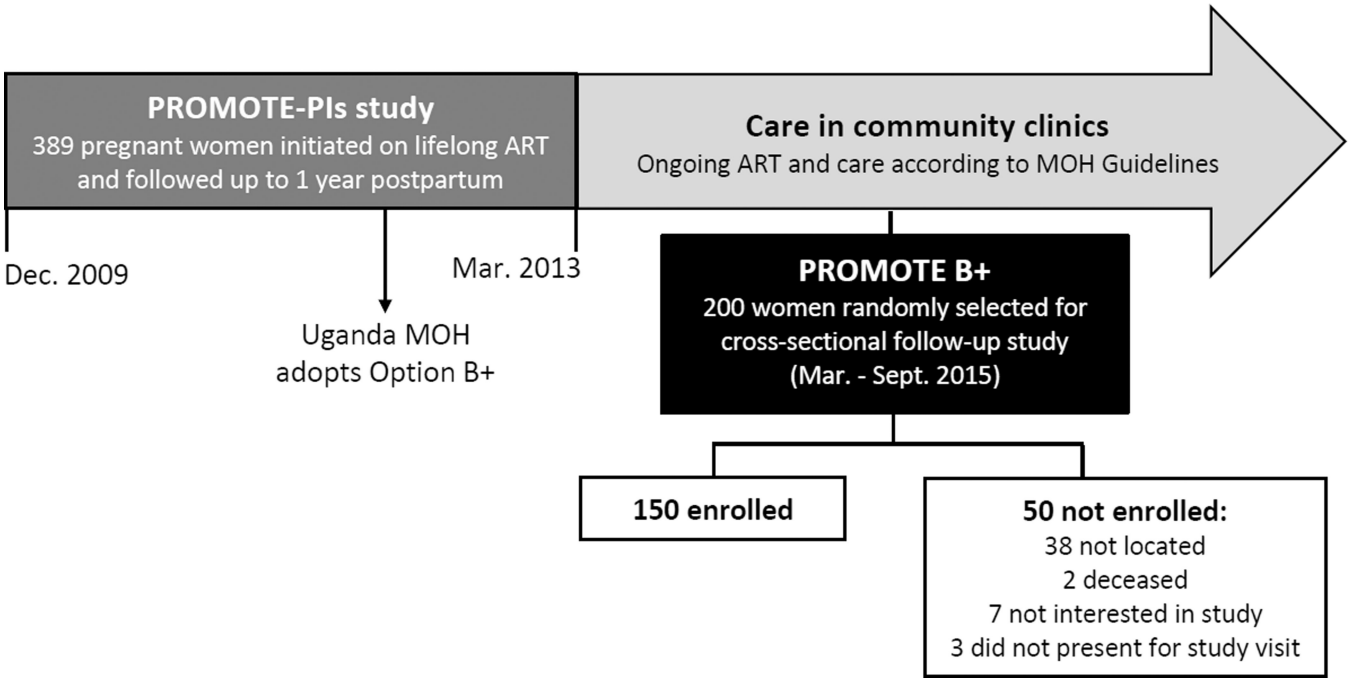

Figure 1. Study schema and enrollment of participants

ART, antiretroviral therapy. MOH, Ministry of Health; PROMOTE-PIs, PROMOTE-Pregnant Women and Infants.

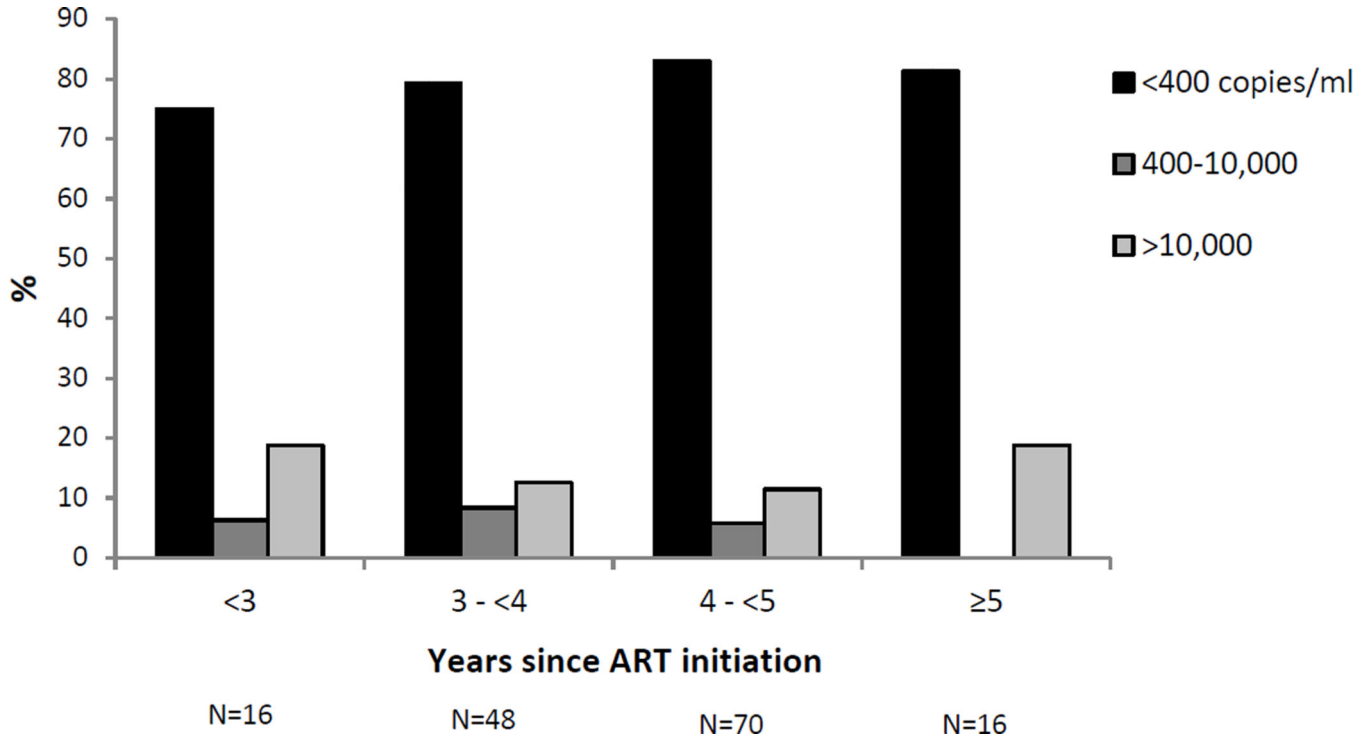

Figure 2. Distribution of HIV-1 RNA results stratified by time in years since ART initiation

Numbers below each column indicate the number of participants in each category of time since ART initiation.

ART, antiretroviral therapy.

Table 1

Characteristics of 150 participants at the time of enrollment in PROMOTE B+

Characteristics of enrolled participants (N= 150)	n (%) or median (IQR)
Age, years	34.5 (29.9–37.6)
Highest level of education completed	
Less than primary	27 (18%)
Primary	101 (67.3%)
Greater than primary	22 (14.7%)
Phone ownership	113 (75%)
Food insufficiency	55 (37%)
No. of living children	4 (3–6)
Years since ART initiation	4.2 (3.4–4.7)
Years postpartum following index pregnancy on ART	3.8 (3.1–4.3)
At least 1 subsequent pregnancy after ART initiation	58 (39%)
Pregnant	19 (13%)
Breastfeeding	23 (15%)
Relationship status	
Single	14 (9%)
Married monogamous	67 (45%)
Married polygamous	53 (35%)
Divorced	8 (5%)
Widowed	8 (5%)
HIV status of primary partner	
Positive	89 (59%)
Negative	28 (19%)
Unknown	22 (15%)
Participant has disclosed HIV status to primary partner	131 (87%)
Most recent CD4 count, cells/mm^3	664 (476–870)
Reports taking ART in prior 3 days	131 (87%)
Current ART regimen[a]	
Efavirenz	78 (59%)
Nevirapine	35 (27%)
Lopinavir	18 (14%)
Receiving care in a government clinic (vs. private or PEPFAR-funded)[b]	87 (63%)

ART, antiretroviral therapy; IQR, inter-quartile range; PEPFAR, President's Emergency Plan for AIDS Relief.

[a]Among participants taking ART

[b]Among participants in care

Table 2

Retention in care and viral suppression among 150 HIV-infected women enrolled in PROMOTE B+

Outcome	n/N	% (95% CI)
Retention in care	135/150	90.0% (84.0–94.3%)
Assign not enrolled to out of care (missing = failure)	135/200	67.5% (60.5–73.9%)
Viral suppression	121/150	80.7% (73.4–86.7%)
Among participants retained in care	121/135	89.6% (83.2–94.2%)
Assign not enrolled to unsuppressed (missing = failure)	121/200	60.5% (53.6–67.3%)

Table 3

Univariate and multivariate analyses of factors associated with viral suppression.

Variable	OR (95% CI)	aOR (95% CI)
HIV status disclosed to primary partner	5.24 (1.21–22.6)	4.51 (1.02–19.8)
Food sufficiency	2.61 (1.00–6.88)	2.27 (0.78–6.59)
Age, per 10 years	1.83 (0.83–4.00)	
Highest level of education completed		
Did not complete primary	ref.	
Primary	0.66 (0.21–2.13)	
Above primary	0.78 (0.17–3.57)	
Phone ownership	0.54 (0.12–2.3)	
PEPFAR-funded/private vs. government clinic	0.68 (0.30–1.57)	
Pregnant or breastfeeding vs. neither	0.98 (0.40–2.44)	
Viral suppression at delivery during index pregnancy on ART	5.0 (0.95–26.4)	
Current ART regimen		
Nevirapine	0.59 (0.17–2.01)	
Lopinavir	1.68 (0.19–14.5)	
Efavirenz	ref.	

aOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; OR, odds ratio; PEPFAR, President's Emergency Plan for AIDS Relief.