Pregnant women with HIV in rural Nigeria have higher rates of antiretroviral treatment initiation, but similar loss to follow-up as non-pregnant women and men

Muktar H. Aliyu^{a,b,*}, Meridith Blevins^{a,c}, Karen M. Megazzini^g, Deidra D. Parrish^{a,b}, Carolyn M. Audet^{a,b}, Naomi Chan^{a,d}, Chisom Odoh^h, Usman I. Gebiⁱ, Mukhtar Y. Muhammadⁱ, Bryan E. Shepherd^{a,c}, C. William Wester^{a,e} and Sten H. Vermund^{a,f}

^aVanderbilt Institute for Global Health; ^bDepartments of Health Policy; ^cDepartment of Biostatistics; ^dDepartment of Human and Organizational Development; ^eDepartment of Medicine; ^fDepartment of Pediatrics, Vanderbilt University, 2525 West End Avenue, Suite 750, Nashville, TN 37203, USA; ^gWestat, Rockville, MD, USA; ^hDepartment of Health Administration and Health Sciences, Tennessee State University, 330 10th Avenue North, Suite D-400, Nashville, TN 37203, USA; ⁱFriends for Global Health Initiative, Abuja, Nigeria

*Corresponding author: Tel: +1 615-343-0626; E-mail: muktar.aliyu@vanderbilt.edu

Received 6 January 2015; revised 31 March 2015; accepted 1 April 2015

Background: We examined antiretroviral therapy (ART) initiation and retention by sex and pregnancy status in rural Nigeria.

Methods: We studied HIV-infected ART-naïve patients aged ≥ 15 years entering care from June 2009 to September 2013. We calculated the probability of early ART initiation and cumulative incidence of loss to follow-up (LTFU) during the first year of ART, and examined the association between LTFU and sex/pregnancy using Cox regression.

Results: The cohort included 3813 ART-naïve HIV-infected adults (2594 women [68.0%], 273 [11.8%] of them pregnant). The proportion of pregnant clients initiating ART within 90 days of enrollment (78.0%, 213/273) was higher than among non-pregnant women (54.3%, 1261/2321) or men (53.0%, 650/1219), both $p < 0.001$. Pregnant women initiated ART sooner than non-pregnant women and men (median [IQR] days from enrollment to ART initiation for pregnant women = 7 days [0–21] vs 14 days [7–49] for non-pregnant women and 14 days [7–42] for men; $p < 0.001$). Cumulative incidence of LTFU during the first year post-ART initiation was high and did not differ by sex and pregnancy status. Persons who were unemployed, bedridden, had higher CD4+ counts, and/or in earlier WHO clinical stages were more likely to be LTFU.

Conclusions: Pregnant women with HIV in rural Nigeria were more likely to initiate ART but were no more likely to be retained in care. Our findings underscore the importance of effective retention strategies across all patient groups, regardless of sex and pregnancy status.

Keywords: Antiretroviral therapy, HIV/AIDS, Loss to follow-up, Nigeria, Retention in care

Introduction

The inclusion of gender-related analysis in medical research is essential to understanding the role of sex and pregnancy on disease outcomes, including differential uptake of health services.^{1–3} Sex-related differences in antiretroviral pharmacokinetics, treatment initiation and adherence, and susceptibility to adverse events are well documented.^{4,5} However, there is considerable variation in the consistency of findings regarding sex differences in initiation of ART. Whereas some studies suggest that men may be more likely to initiate ART than women^{6–8} or vice versa,⁹ others do not show any differences.^{10–12} In addition, recent studies from sub-Saharan Africa,^{13–15} including Nigeria,¹⁶ suggest

that male sex may be an important predictor of mortality in HIV-infected adults, partly because men enter ART programs with more advanced disease and lower CD4+ cell counts.^{13,17–23}

Now that WHO advocates for the Option B+ strategy (placing HIV-infected pregnant women on lifelong ART) for programmatic and operational reasons (particularly in settings with generalized epidemics), and the African programs supported by the U.S. President's Plan for AIDS Relief (PEPFAR) are advocating Option B+ when national Ministries of Health adopt it, outcomes research from sub-Saharan Africa must consider sex and pregnancy-based differences.

The objective of this study was to examine whether sex and pregnancy differences exist in ART initiation and in retention in

care in a cohort of people with HIV enrolled in a large comprehensive HIV treatment program in rural north central Nigeria. HIV treatment programs in Nigeria and other parts of sub-Saharan Africa continue to face challenges in timely uptake of ART and retention in care.^{24–26} Findings from this study can illuminate the potential challenges that could confront implementation of HIV treatment initiatives like Option B+, and reveal how early ART initiation and retention of pregnant patients compares to programmatic indicators for non-pregnant women and men in the same rural, resource-limited setting.

Materials and methods

Study area and population

In 2008 Vanderbilt University received a 5-year award via the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) to support the implementation of comprehensive HIV/AIDS care and treatment programs in Kwara and Niger states of north central Nigeria. Nigeria's north central region has the highest HIV prevalence among pregnant women in the country (2010 HIV prevalence among antenatal clinic attendees of 7.5% vs 3.6% nationally).²⁷ However, HIV prevalence among all adults living in the region (15 years and older) is similar to the national average (about 3.4%).²⁸ Friends in Global Health (FGH), a non-governmental organization affiliated with Vanderbilt University, served as the primary implementation body. Over the study period, FGH supported HIV treatment services in five hospitals: Sobi Specialist Hospital and Lafiagi General Hospital in Kwara state; and Gawu Babangida Rural Hospital, Kuta Rural Hospital, and Umaru Yar Adua Hospital, in Niger State. These five hospitals were served by nine feeder sites in a 'spoke-hub' distribution model that provided HIV testing and counseling (HTC) and prevention of mother-to-child HIV transmission (PMTCT) services.

Care and treatment protocol

Care and treatment protocol in the Vanderbilt University (VU)/FGH program has been previously detailed.²⁹ All enrolled patients received an initial evaluation, including baseline labs (CD4+ cell count [CD4 count], hematology, chemistry), WHO clinical staging and a clinical exam. Clients also received a basic care kit, adherence counseling, nutritional support, palliative care and home-based care services (based on need). Adult patients were deemed eligible for ART based on Nigerian guidelines, i.e., WHO clinical stage I/II disease with CD4 count <200 cells/ μ L; WHO clinical stage III disease with CD4 count 200–350 cells/ μ L, or WHO clinical stage IV disease irrespective of CD4 count. The most common adult ART regimen was a combination of zidovudine (or tenofovir in more recent years) plus lamivudine (or emtricitabine) plus efavirenz (non-pregnant clients) or nevirapine. Pregnant women who tested HIV-positive were offered antiretroviral prophylaxis or treatment, consistent with national guidelines. Non-pregnant patients were followed up every 1–3 months, while pregnant women were seen monthly or more frequently, depending on gestational age.

Data collection and statistical analysis

This study used routine clinical data collected in September 2013 and included ART-naïve HIV-infected patients entering HIV care

and treatment at age ≥ 15 years. Each clinic day, clerks entered data from clinical forms into CAREWare (JPROG, New Orleans, LA, USA), an electronic medical records system. Routine audits of medical records were performed to ensure forms were completed accurately and laboratory data entered correctly. Data queries for out-of-range and missing data were addressed by each site and the clean data were extracted for final analyses. Our primary outcome was difference in ART initiation and retention by sex among enrolled clients and ART initiators between June 2009 and September 2013. LTFU was defined as no contact with the clinic in the 180 days prior to database closure with no report of death. This definition is roughly consistent with the Nigerian standard for LTFU of >90 days late to a scheduled visit (given that visits are scheduled at least every 3 months). Because next scheduled visit date is not captured in the database and routine visits may be spaced up to 3 months apart, we counted 180 days from 3 months past the last contact so as not to overcount LTFU. Patients who dropped out regardless of duration, but re-engaged in care during the study period were not counted as LTFU. For ART commencement in the first 90 days, time was measured from date of enrollment to date of ART initiation. Time was measured from the ART initiation date to the earliest of the date last known alive or 365 days after treatment initiation. Date last known alive was ascertained by date of death or the latest date of clinical observation, laboratory result, or pharmacy visit. Pregnant clients were identified through a record of 'currently pregnant' within 90 days before or 30 days after enrollment into HIV care.

Descriptive statistics were tabulated by sex and pregnancy status. Kruskal Wallis and χ^2 tests were used to compare differences in baseline characteristics by sex and pregnancy status. Kaplan-Meier and cumulative incidence estimates (treating death as a competing risk) were calculated for early ART initiation and LTFU by sex and pregnancy status. Multivariable Cox regression was used to estimate risk factors associated with LTFU during the first 12 months of ART. Multiple imputation with predictive mean matching and 25 imputation data sets was used in the Cox regression to account for missing values in covariates and to prevent case-wise deletion of missing data.³⁰ Covariates were selected a priori, including: sex and pregnancy status, age, educational level, marital status, employment status, body mass index (BMI), functional status (working, ambulatory, or bedridden), CD4 count, and WHO clinical stage. Nonlinearity assumptions were investigated for age, BMI, and CD4 count. No serious departures from linearity were found. Patient follow-up among those who died before 12 months was censored at date of death.

Our hypotheses were: pregnant women would start timely ART at a higher rate owing to less stringent initiation criteria and the focus on prevention of HIV transmission to the child; and pregnant women would have better retention on ART than non-pregnant women and men. We employed R-software 3.0.2 (www.r-project.org) and an 'intent-to-continue-treatment' approach for all data analyses.

Results

A total of 3813 ART-naïve adult clients (68.0%, 2594/3813 women, 10.5% or 273/2594 of whom were pregnant) were enrolled into HIV care and treatment across the five VU/FGH-supported sites

Table 1. Demographics and clinical characteristics of patients by sex and pregnancy status, VU/FGH Program, Nigeria, 2009–2013

	Sex and pregnancy status				p-value
	Pregnant female n=273	Non-pregnant female n=2321	Male n=1219	Combined n=3813	
Clinic, n (%)					<0.001
GBRH	34 (12.5)	459 (19.8)	279 (22.9)	772 (20.2)	
Kuta	2 (0.8)	64 (2.7)	38 (3.1)	104 (2.7)	
LGH	45 (16.5)	334 (14.4)	126 (10.3)	505 (13.2)	
SBSH	70 (25.6)	567 (24.4)	265 (21.7)	902 (23.6)	
UMYMH	122 (44.7)	897 (38.6)	511 (41.9)	1530 (40.1)	
Age, years, median (IQR)	27 (24–30)	30 (25–37)	38 (32–44)	32 (27–40)	<0.001
Education, n (%)					<0.001
Missing	58 (21.4)	848 (36.5)	460 (37.7)	1366 (35.8)	
None	79 (36.7)	624 (42.3)	206 (27.1)	909 (37.1)	
Primary	64 (29.8)	393 (26.7)	222 (29.2)	679 (27.7)	
Post-secondary	11 (5.1)	109 (7.4)	81 (10.7)	201 (8.5)	
Secondary	61 (28.4)	347 (23.5)	250 (32.9)	658 (26.9)	
Marital status, n (%)					<0.001
Missing	44 (16.1)	701 (30.2)	393 (32.2)	1138 (29.8)	
Divorced/Separated	6 (2.6)	116 (7.2)	24 (2.9)	146 (5.5)	
Married	212 (92.6)	1205 (74.4)	706 (85.5)	2123 (79.4)	
Single	7 (3.1)	155 (9.6)	78 (9.4)	240 (9.0)	
Widowed	4 (1.7)	144 (8.9)	18 (2.2)	166 (6.2)	
Occupation, n (%)					<0.001
Missing	51 (18.7)	749 (32.3)	401 (32.9)	1201 (31.5)	
Employed	53 (23.9)	275 (17.5)	351 (42.9)	679 (26.0)	
Other	22 (9.9)	244 (15.5)	104 (12.7)	370 (14.2)	
Unemployed	147 (66.2)	1053 (67.0)	363 (44.4)	1563 (59.8)	
BMI, kg/m ² , median (IQR)	22.3 (20.5–246)	20.6 (18.4–23.5)	20.5 (18.4–22.7)	20.8 (18.5–23.4)	<0.001
Missing BMI, kg/m ² , n (%)	97 (35.5)	903 (38.9)	471 (38.6)	1471 (38.6)	
CD4+ cell count, cells/μL, median (IQR)	306 (174–475)	244 (121–415)	197 (91–328)	232 (114–390)	<0.001
Missing CD4 count, n (%)	44 (16.1)	375 (16.1)	226 (18.5)	645 (16.9)	
CD4 count category, n (%)					
Missing	44 (16.1)	375 (16.1)	226 (18.5)	645 (16.9)	
<50 cells/μL	10 (4.4)	177 (9.1)	111 (11.2)	298 (9.4)	
51–200 cells/μL	58 (25.3)	646 (33.2)	393 (39.6)	1097 (34.6)	
201–350 cells/μL	62 (27.1)	484 (24.9)	273 (27.5)	819 (25.8)	
>350 cells/μL	99 (43.2)	639 (32.8)	216 (21.7)	954 (30.1)	
WHO stage, n (%)					<0.001
Missing	14 (5.1)	178 (7.7)	96 (7.9)	288 (7.7)	
I	197 (76.1)	1110 (51.8)	463 (41.2)	1770 (50.2)	
II	41 (15.8)	434 (20.3)	271 (24.1)	746 (21.2)	
III	21 (8.1)	540 (25.2)	352 (31.3)	913 (25.9)	
IV	0	59 (2.8)	37 (3.3)	96 (2.7)	
ART status, n (%)					<0.001
ART >90 days from enrollment	14 (5.1)	229 (9.9)	102 (8.4)	345 (9.0)	
ART in 90 days from enrollment	213 (78.0)	1261 (54.3)	650 (53.3)	2124 (55.7)	
No ART	46 (16.8)	831 (35.8)	467 (38.3)	1344 (35.2)	
Death in 12 months (enrollment), n (%)	0	49 (2.1)	43 (3.5)	92 (2.4)	
Lost in 12 months (enrollment), n (%)	180 (65.9)	1505 (64.8)	815 (66.9)	2500 (65.6)	

ART: antiretroviral therapy; BMI: body mass index; GBRH: Gawu Babangida Rural Hospital; Kuta: Rural Hospital, Kuta; LGH: Lafiagi General Hospital; SBSH: Sobi Specialist Hospital; UMYMH: Umaru YarAdua Memorial Hospital, Sabon-Wuse; VU/FGH: Vanderbilt University/Friends in Global Health.

between 1 June 2009 and 30 September 2013 (Table 1). The majority of clients were married (79.4%, 2123/2675), unemployed (659.8%, 1563/2612) and enrolled in either Umaru Yar Adua Hospital (40.1%, 1530/3813) or Sobi Specialist Hospital (23.7%, 902/3813). Pregnant women enrolled into care were younger than their non-pregnant and male counterparts (median age [IQR] = 27 [24–30] years vs 30 [25–37] years and 38 [32–44] years, respectively, $p < 0.001$). At enrollment, pregnant women had higher median CD4 counts (306 cells/ μ L [IQR 174–475]) than non-pregnant women (244 cells/ μ L [IQR 121–415]), and men (197 cells/ μ L [IQR: 91–328]), $p < 0.001$.

Slightly more than half (55.7%, 2124/3813) of all enrolled clients initiated ART within 90 days of enrollment. The proportion of pregnant clients initiating ART within 90 days of enrollment (78.0%, 213/273) was significantly higher than the corresponding proportion of non-pregnant women (54.3%, 1261/2321) and men (53.3%, 650/1219), $p < 0.001$ (Figure 1A). The proportion of pregnant clients initiating ART within 90 days of enrollment (78.0%, 213/273) remained significantly higher than the corresponding proportion of non-pregnant women (70.2%, 963/1371) and men (64.4%, 534/829) after including only clients that are determined to be ART eligible based on pregnancy status, WHO clinical stage, or CD4 count at enrollment, $p < 0.001$ (Figure 1B). Time from enrollment to ART initiation was also significantly shorter for pregnant women (median [IQR] 7 days [0–21]) compared to non-pregnant women (14 days [7–49]) and men (14 days [7–42]) ($p < 0.001$).

Among patients initiating ART within 90 days of enrollment ($n = 2124$), the cumulative incidence of LTFU during the first 12 months of ART was very high (63%). No significant difference was observed between the groups in cumulative incidence of LTFU during the first 12 months following ART initiation (65% of pregnant women vs 63% of non-pregnant women and 62% of men), $p = 0.79$ (Figure 1C). In multivariable Cox regression, we modeled the association between sex and pregnancy status and 12-month retention adjusting for age, level of education, marital and employment status, BMI, functional status, CD4 count, and WHO clinical stage (Table 2). We failed to detect a

statistical association of sex and pregnancy group with LTFU during the first 12 months on ART, although the point estimates of 9% higher hazard in males and 7% lower hazard in pregnant females compared with non-pregnant females align with our a priori hypothesis. Factors independently associated with LTFU in our population included employment status, functional status, and WHO clinical stage. An employed patient had a 31% lower hazard of LTFU than someone who was unemployed (adjusted hazard ratio [AHR] 95% CI 0.69 [0.56–0.85]; $p < 0.001$). A bedridden individual had 72% higher hazard of LTFU compared with working functional status (AHR 95% CI 1.72 [1.02–2.87]; $p = 0.02$). Lower CD4 count and more advanced stage of HIV disease were independently associated with lower hazards of LTFU ($p = 0.005$ and $p = 0.001$, respectively). The hazard of LTFU was 11% less for patients starting ART with CD4 of 50 versus 200 cells/ μ L (AHR 95% CI 0.89 [0.82–0.97]; $p = 0.005$). Mortality after 12 months on ART was low across all three groups: no deaths were recorded among pregnant women, whereas men had twice the mortality rate of non-pregnant women (4% vs 2%).

Discussion

HIV/AIDS programs in sub-Saharan Africa have historically focused on pregnant women attending antenatal clinics. Recently, programs have extended their focus to male partners in an effort to improve uptake of and long-term adherence to treatment, given that socioeconomic and health decision-making power is skewed in favor of men.^{31–33} In this large prospective study, we report sex and pregnancy-related disparities in timely initiation of ART, with men and non-pregnant women both initiating ART at lower rates when compared to pregnant women. Our findings are consistent with other reports^{6–9,23,34} and are likely a reflection of earlier testing of pregnant women for PMTCT, sex differences in health-seeking behavior, increased visit intensity/frequency, as well as a greater perceived need for care in pregnancy.¹ Other factors include fear of stigma/discrimination, the historic emphasis of HIV services in Africa on women and children,³⁵ and gender stereotypes.^{1,13} There is a need for multi-

Figure 1. (A) Antiretroviral therapy (ART) initiation during the first 90 days after enrollment by gender and pregnancy status, Vanderbilt University/Friends in Global Health (VU/FGH) Nigeria Program, 2009–2013; (B) ART initiation among ART eligible clients during the first 90 days after enrollment by gender and pregnancy status, VU/FGH Nigeria Program, 2009–2013; (C) Cumulative incidence of loss to follow-up during the first 12 months following ART initiation by gender and pregnancy status at enrollment, VU/FGH Nigeria program (for individuals who were initiated on ART within 90 days of enrollment, $n = 2124$). Solid line: pregnant females; dashed lines: nonpregnant females; dotted lines: males. This figure is available in black and white in print and in colour at International Health online.

Table 2. Cox regression of loss to follow-up during 12 months on antiretroviral therapy (n=2124), VU/FGH Nigeria Program, 2009–2013

	Hazard ratio (95% CI)	p-value
Age (per 5 yrs)	1.00 (0.97–1.03)	NS
Sex and pregnancy status		NS
Non-pregnant female (ref)	1	
Pregnant female	0.93 (0.76–1.13)	
Male	1.09 (0.91–1.28)	
Education		NS
None (ref)	1	
Primary	1.08 (0.91–1.28)	
Secondary	1.20 (1.01–1.43)	
Post-secondary	1.28 (0.97–1.68)	
Marital status		NS
Married (ref)	1	
Divorced/separated	1.07 (0.82–1.39)	
Single	1.04 (0.80–1.37)	
Widowed	0.99 (0.75–1.30)	
Occupational status		<0.001
Unemployed (ref)	1	
Employed	0.69 (0.56–0.85)	
Other	1.10 (0.89–1.36)	
BMI (per 1 kg/m ²)	0.99 (0.97–1.01)	NS
Functional status		0.019
Working (ref)	1	
Ambulatory	1.27 (1.02–1.59)	
Bedridden	1.72 (1.02–2.87)	
CD4 count (cells/μL)		0.005
50 vs 200	0.89 (0.82–0.97)	
350 vs 200	1.08 (1.02–1.13)	
500 vs 200	1.14 (1.04–1.25)	
WHO stage		0.001
I (ref)	1	
II	0.87 (0.75–1.02)	
III	0.72 (0.61–0.85)	
IV	0.79 (0.51–1.23)	

BMI: body mass index; VU/FGH: Vanderbilt University/Friends in Global Health.

pronged programs that will ensure equitable access to and uptake of ART for men without prejudice to other population groups.³⁵ Such programs could incorporate community-based components that address cultural concepts of masculinity, that encourage male engagement and thereby increase utilization of HIV services by men, and that create innovative approaches to reaching men and providing them with care in a variety of settings (e.g., workplaces and social venues). Building the cultural competency skills of health workers and community volunteers through training opportunities coupled with targeted funding of programs that prioritize considerations of traditional gender norms will also help create health systems that foster an enabling environment for positive male engagement in ART programs.

Rates of LTFU in our cohort did not vary by sex or pregnancy status. Pregnant women dropped out of treatment at similarly high rates as non-pregnant women and men, despite initiating ART in a more timely fashion. This finding is similar to recent results from Ethiopia,³⁶ but conflicts with reports of higher rates of LTFU among men in Nigeria^{25,37} and other places.^{38–40} Our LTFU rates are also substantially higher than rates from similar public ART programs in Nigeria,^{25,26,41} and other parts of Africa.^{23,42} Given the relatively low mortality rate in our cohort, it is possible that a sizeable proportion of our LTFU population may have actually died, consistent with observations from south-east Nigeria²⁶ and elsewhere.^{43,44} In addition, our group⁴⁵ and others^{46–48} have shown that widely varying estimates for LTFU can result from differences in underlying assumptions used to define LTFU. Nevertheless, retention in care is the cornerstone of effective HIV/AIDS treatment programs,²⁰ and the very high attrition rate depicted here should raise concerns about the quality and effectiveness of HIV/AIDS programs in rural Nigeria. The WHO Option B+ approach suggests that ART initiated in pregnant women and continued lifelong can maximize both the PMTCT and also women's health. Our work suggests that Option B+ will increase ART initiation, but does not suggest that the LTFU rate for pregnant women will be any different to that from non-pregnant women or men, underscoring the urgency of effective retention strategies for the success of the Option B+ approach beyond PMTCT for the health of women themselves. The health system challenges that impact provision of quality and timely HIV services to men and non-pregnant women will also influence service delivery to new mothers after they give birth. In rural Nigeria such considerations require the development of cost-effective initiatives that will harness existing community resources (human and fiscal) while emphasizing practicality and sustainability. Encouraging the active involvement of community members in HIV program implementation (including monitoring and evaluation activities) will foster a sense of ownership and reinforce positive community perceptions of the value of such programs.

We found unemployment, poor functional status, higher CD4 counts, and earlier WHO clinical stage to be independently associated with LTFU. Individuals who were gainfully employed were 31% less likely to drop out of care compared to those who were unemployed. Employment status is likely a proxy for other measures that impact retention. For example, unemployed persons are less likely to be in steady relationships, to have stable housing, or to afford the incidental costs associated with securing health care.⁴⁹ Our report of lower risk of LTFU in persons with higher functional status (working vs ambulatory or bedridden) parallels our findings as regards employment status and confirms results from another Nigeria cohort.⁵⁰ The higher risk of LTFU among patients in WHO clinical stage I vs higher clinical stages also corroborates a similar report from Ethiopia.³⁶ However, our findings that individuals with higher CD4 counts were more likely to be LTFU is consistent with some reports^{36,51} but not with others.^{52–54} A similar study from Nigeria²⁵ found an increased risk of LTFU in patients with low (<100) and high (>350) CD4 counts, which the authors attributed to patients being dead, or believing themselves to be healthy and therefore not needing to return for care.

Our study has the following strengths: a large sample size, a relatively culturally homogenous population, and our use of routine program data from the 'real world' setting of rural north

central Nigeria. A limitation of this study is our lack of knowledge of patient transfers, as that information is not routinely collected. It is possible that some pregnant women classified as LTFU may have discontinued ART after delivery and returned to their maternal and child health clinic for routine postpartum care. In addition, there is potential for misclassification of LTFU, since death ascertainment is low. However, we believe that any misclassification did not vary by sex or pregnancy status and therefore is not likely to impact our conclusions. Also, our findings may not generalize to other settings. Nevertheless, our cohort is drawn from a rural, low-resourced environment that is typical of many other parts of sub-Saharan Africa. Some of the differences in ART initiation could be explained by increased visit intensity and frequency among pregnant women. We are also unable to assess ART adherence using objective measures (e.g., medication possession ratio), as such data are not routinely collected.

Conclusions

We report earlier ART initiation but similar rates of LTFU during the first year of ART among pregnant women vs non-pregnant women and men in north central Nigeria. HIV care is optimized when interventions engage and empower men and women, support program implementation, and confront the sociocultural and economic barriers that facilitate continued transmission of HIV. The integration of gender into HIV programming, including policy considerations that will combat inequities in access and uptake of ART services, should be a priority of national programs. The best multi-sectoral approaches to scaling up ART services while combating LTFU in similarly challenging environments remain to be developed. Such approaches are especially vital in this era of Option B+ strategies and earlier initiation of ART for clinical benefits and for ‘treatment as prevention’.

Authors’ contributions: MA, MB, DP, KM and CWW conceived the study. MA, MB, MM, UG, CO and KM contributed to study implementation and data interpretation. MB performed the data analysis. BS, CA, CWW and SHV critically revised the manuscript for intellectual content. All authors contributed to writing the manuscript. All authors read and approved the final version of the paper. MA and MB are the guarantors of this paper.

Acknowledgements: We acknowledge Julie Lankford, Dr Saidu Ishaq, Anne Neubecker and Adiba Hassan and our numerous in-country staff who contributed to the successful implementation of this study.

Funding: This work was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health [R01HD075075] and the Fogarty Clinical Research Fellows Program [R24TW007988]. CA is supported in part by Clinician and Translational Science Award [CTSA]/Vanderbilt Clinical & Translational Research Scholars grant [KL2TR000445]. The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of the National Institutes of Health.

Competing interests: None declared.

Ethical approval: Ethical approval was obtained from the Nigeria National Human Research Ethics Committee. The study was classified as exempt by the Vanderbilt University Institutional Review Board.

References

- 1 Heidari S, Abdool Karim Q, Auerbach JD et al. Gender-sensitive reporting in medical research. *J Int AIDS Soc* 2012;15:11.
- 2 d’Arminio Monforte A, González L, Haberl A et al. Women for Positive Action. Better mind the gap: addressing the shortage of HIV-positive women in clinical trials. *AIDS* 2010;24:1091–4.
- 3 Taking sex into account in medicine. *Lancet* 2011;378:1826.
- 4 Nicastrì E, Leone S, Angeletti C et al. Sex issues in HIV-1-infected persons during highly active antiretroviral therapy: a systematic review. *J Antimicrob Chemother* 2007;60:724–32.
- 5 Floridia M, Giuliano M, Palmisano L, Vella S. Gender differences in the treatment of HIV infection. *Pharmacol Res* 2008;58:173–82.
- 6 Geng EH, Hunt PW, Diero LO et al. Trends in the clinical characteristics of HIV-infected patients initiating antiretroviral therapy in Kenya, Uganda and Tanzania between 2002 and 2009. *J Int AIDS Soc* 2011;14:46.
- 7 Gebo KA, Fleishman JA, Conviser R et al. Racial and gender disparities in receipt of highly active antiretroviral therapy persist in a multistate sample of HIV patients in 2001. *J Acquir Immune Defic Syndr* 2005;38:96–103.
- 8 Giordano TP, White AC Jr, Sajja P et al. Factors associated with the use of highly active antiretroviral therapy in patients newly entering care in an urban clinic. *J Acquir Immune Defic Syndr* 2003;32:399–405.
- 9 Kober C, Johnson M, Fisher M et al. Non-uptake of highly active antiretroviral therapy among patients with a CD4 count < 350 cells/μL in the UK. *HIV Med* 2012;13:73–8.
- 10 McDonald K, Bartos M, Rosenthal D. Australian women living with HIV/AIDS are more sceptical than men about antiretroviral treatment. *AIDS Care* 2001;13:15–26.
- 11 Fardet L, Mary-Krause M, Heard I et al. French Hospital Database on HIV. Influence of gender and HIV transmission group on initial highly active antiretroviral therapy prescription and treatment response. *HIV Med* 2006;7:520–9.
- 12 McNaghten AD, Hanson DL, Dworkin MS, Jones JL. Adult/Adolescent Spectrum of HIV Disease Group. Differences in prescription of antiretroviral therapy in a large cohort of HIV-infected patients. *J Acquir Immune Defic Syndr* 2003;32:499–505.
- 13 Chen SC, Yu JK, Harries AD et al. Increased mortality of male adults with AIDS related to poor compliance to antiretroviral therapy in Malawi. *Trop Med Int Health* 2008;13:513–9.
- 14 Taylor-Smith K, Tweya H, Harries A et al. Gender differences in retention and survival on antiretroviral therapy of HIV-1 infected adults in Malawi. *Malawi Med J* 2010;22:49–56.
- 15 Mills EJ, Bakanda C, Birungi J et al. Male gender predicts mortality in a large cohort of patients receiving antiretroviral therapy in Uganda. *J Int AIDS Soc* 2011;14:52.
- 16 Agaba PA, Digin E, Makai R et al. Clinical characteristics and predictors of mortality in hospitalized HIV-infected Nigerians. *J Infect Dev Ctries* 2011;5:377–82.
- 17 Agaba PA, Meloni ST, Sule HM et al. Patients who present late to HIV care and associated risk factors in Nigeria. *HIV Med* 2014;15:396–405.
- 18 Braitstein P, Brinkhof MW, Dabis F et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* 2006;367:817–24. Erratum in: *Lancet* 2006;367:1902.
- 19 Stringer JS, Zulu I, Levy J et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. *JAMA* 2006;296:782–93.

- 20 Boulle A, Bock P, Osler M et al. Antiretroviral therapy and early mortality in South Africa. *Bull World Health Organ* 2008;86:678–87.
- 21 Braitstein P, Boulle A, Nash D et al. Gender and the use of antiretroviral treatment in resource-constrained settings: findings from a multicenter collaboration. *J Womens Health (Larchmt)* 2008;17:47–55.
- 22 ART-LINC Collaboration of International Databases to Evaluate AIDS (IeDEA) Keiser O, Anastos K, Schechter M et al. Antiretroviral therapy in resource-limited settings 1996 to 2006: patient characteristics, treatment regimens and monitoring in sub-Saharan Africa, Asia and Latin America. *Trop Med Int Health* 2008;13:870–9.
- 23 Cornell M, Myer L, Kaplan R et al. The impact of gender and income on survival and retention in a South African antiretroviral therapy programme. *Trop Med Int Health* 2009;14:722–31.
- 24 Aliyu MH, Varkey P, Salihu HM et al. The HIV/AIDS epidemic in Nigeria: progress, problems and prospects. *Afr J Med Med Sci* 2010;39:233–9.
- 25 Charurat M, Oyegunle M, Benjamin R et al. Patient retention and adherence to antiretrovirals in a large antiretroviral therapy program in Nigeria: a longitudinal analysis for risk factors. *PLoS One*. 2010;5:e10584.
- 26 Onoka CA, Uzoichukwu BS, Onwujekwe OE et al. Retention and loss to follow-up in antiretroviral treatment programmes in southeast Nigeria. *Pathog Glob Health* 2012;106:46–54.
- 27 Federal Ministry of Health, Nigeria (FMOH). National AIDS/STI Control Program. Technical Report. 2010 National HIV Sero-prevalence Sentinel Survey. Abuja; Federal Ministry of Health; 2010. http://www.nigeria-aids.org/documents/2010_National%20HIV%20Sero%20Prevalence%20Sentinel%20Survey.pdf Accessed 9 October 2014.
- 28 Federal Ministry of Health (Nigeria). National HIV/AIDS and Reproductive Health Survey 2012 (NARHS Plus II): Human immunodeficiency virus Testing. *J HIV Hum Reprod* 2014;2:15–29.
- 29 Aliyu MH, Blevins M, Parrish DD et al. Risk factors for delayed initiation of combination antiretroviral therapy in rural north central Nigeria. *J Acquir Immune Defic Syndr* 2014;65:e41–9.
- 30 Harrell FE Jr, Dupont MC. Package 'Hmisc'. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. 2012.
- 31 Aarnio P, Olsson P, Chimbiri A, Kulmala T. Male involvement in antenatal HIV counseling and testing: exploring men's perceptions in rural Malawi. *AIDS Care* 2009;21:1537–46.
- 32 Dunlap J, Foderingham N, Bussell S et al. Male involvement for the prevention of mother-to-child HIV transmission: A brief review of initiatives in East, West, and Central Africa. *Curr HIV/AIDS Rep* 2014;11:109–18.
- 33 Nyondo AL, Chimwaza AF, Muula AS. Stakeholders' perceptions on factors influencing male involvement in prevention of mother to child transmission of HIV services in Blantyre, Malawi. *BMC Public Health* 2014;14:691.
- 34 Cornell M, Schomaker M, Garone DB et al. Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: a multicentre cohort study. *PLoS Med* 2012;9:e1001304.
- 35 Cornell M, McIntyre J, Myer L. Men and antiretroviral therapy in Africa: our blind spot. *Trop Med Int Health*. 2011;16:828–9.
- 36 Berheto TM, Haile DB, Mohammed S. Predictors of loss to follow-up in patients living with HIV/AIDS after initiation of antiretroviral therapy. *N Am J Med Sci* 2014;6:453–9.
- 37 Odafe S, Torpey K, Khamofu H et al. The pattern of attrition from an antiretroviral treatment program in Nigeria. *PLoS One*. 2012;7:e1254.
- 38 Molfino L, Kumar AM, Isaakidis P et al. High attrition among HIV-infected patients with advanced disease treated in an intermediary referral center in Maputo, Mozambique. *Glob Health Action* 2014;7:23758.
- 39 Mutasa-Apollo T, Shiraishi RW, Takarinda KC 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:e86305.
- 40 Blevins M, Jos E, Bilhete FR et al. Two-year death and loss to follow-up outcomes by source of referral to HIV care for HIV-infected patients initiating antiretroviral therapy in rural Mozambique. *AIDS Res Hum Retroviruses* 2015;31:198–207.
- 41 Ojikutu B, Higgins-Biddle M, Greeson D et al. The association between quality of HIV care, loss to follow-up and mortality in pediatric and adolescent patients receiving antiretroviral therapy in Nigeria. *PLoS One* 2014;9:e100039.
- 42 Van Cutsem G, Ford N, Hildebrand K et al. Correcting for mortality among patients lost to follow up on antiretroviral therapy in South Africa: a cohort analysis. *PLoS One* 2011;6:e14684.
- 43 Bisson GP, Gaolathe T, Gross R et al. Overestimates of survival after HAART: implications for global scale-up efforts. *PLoS One* 2008;3:e1725.
- 44 Yu JK, Chen SC, Wang KY et al. True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi. *Bull World Health Organ* 2007;85:550–4.
- 45 Shepherd BE, Blevins M, Vaz LM et al. Impact of definitions of loss to follow-up on estimates of retention, disease progression, and mortality: application to an HIV program in Mozambique. *Am J Epidemiol* 2013;178:819–28.
- 46 Li MS, Musonda P, Gartland M et al. Predictors of patient attrition according to different definitions for loss to follow-up: a comparative analysis from Lusaka, Zambia. *J Acquir Immune Defic Syndr* 2013;63:e116–9.
- 47 Chi BH, Yiannoutsos CT, Westfall AO et al. Universal definition of loss to follow-up in HIV treatment programs: a statistical analysis of 111 facilities in Africa, Asia, and Latin America. *PLoS Med* 2011;8:e1001111.
- 48 Grimsrud AT, Cornell M, Egger M et al. Impact of definitions of loss to follow-up (LTFU) in antiretroviral therapy program evaluation: variation in the definition can have an appreciable impact on estimated proportions of LTFU. *J Clin Epidemiol* 2013;66:1006–13.
- 49 Bartley M. Unemployment and ill health: understanding the relationship. *J Epidemiol Community Health* 1994;48:333–337.
- 50 Odafe S, Idoko O, Badru T et al. Patients' demographic and clinical characteristics and level of care associated with lost to follow-up and mortality in adult patients on first-line ART in Nigerian hospitals. *J Int AIDS Soc* 2012;15:17424.
- 51 Arici C, Ripamonti D, Maggiolo F et al. Factors associated with the failure of HIV-positive persons to return for scheduled medical visits. *HIV Clin Trials* 2002;3:52–7.
- 52 Alvarez-Uria G, Naik PK, Pakam R, Midde M. Factors associated with attrition, mortality, and loss to follow up after antiretroviral therapy initiation: data from an HIV cohort study in India. *Glob Health Action* 2013;6:21682.
- 53 Schni-Affolter F, Keiser O, Mwango A et al. Swiss HIV Cohort Study; IeDEA Southern Africa. Estimating loss to follow-up in HIV-infected patients on antiretroviral therapy: the effect of the competing risk of death in Zambia and Switzerland. *PLoS One* 2011;6:e27919.
- 54 Hill T, Bansil L, Sabin C et al. Data linkage reduces loss to follow-up in an observational HIV cohort study. *J Clin Epidemiol* 2010;63:1101–9.