Antiretroviral Therapy Initiation for Treatment and Prevention in East Africa

Andrew Mujugira

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2013

Committee:

Jared Baeten

Connie Celum

Carey Farquhar

Program authorized to offer degree: Public Health-Epidemiology

University of Washington

Abstract

Antiretroviral Therapy Initiation for Treatment and Prevention in East Africa

Andrew Mujugira

Chair of the Supervisory Committee:

Associate Professor Jared Baeten

Epidemiology

In serodiscordant couples, provision of antiretroviral therapy (ART) to the HIV-infected partner significantly decreases risk of sexual HIV transmission of HIV. The World Health Organization has recently issued guidelines recommending ART initiation, regardless of CD4 count, for HIV-infected members of serodiscordant couples to prevent HIV transmission to the uninfected partner. We conducted a prospective cohort study among 1998 HIV-infected individuals with known HIV-uninfected partners who were enrolled in the Partners PrEP Study, an HIV prevention clinical trial in Kenya and Uganda. The primary objective was to assess ART initiation in those who became ART-eligible during study follow-up. The cumulative probabilities of initiating ART at 6, 12, and 24 months after referral were 60.8%, 78.8% and 91.5%, respectively. Approximately 40% of HIV-infected partners had not initiated ART six months after initial referrals. Higher CD4 ($p<0.001$), asymptomatic HIV disease ($p=0.04$), and alcohol use ($p=0.001$) were significant predictors of ART initiation.

To evaluate whether HIV-infected persons would be interested in earlier ART (CD4 >350 cells/μL) for HIV prevention, as recommended by the WHO, we conducted a cross-sectional study among an additional 571 East African HIV-infected individuals in serodiscordant partnerships. The objective of the study was to determine whether fertility intentions were correlated with a greater likelihood to initiate early ART for

prevention. We found that HIV-infected partners with fertility intentions were nearly twice as likely to express interest in early ART for HIV prevention (adjusted odds ratio [aOR] 1.83, p=0.02) than those without fertility intentions. Younger age (p<0.001), male sex (p=0.05), lack of children in the partnership (p=0.002), and unprotected sex in the prior month (p=0.05) were associated with fertility intentions among HIV-infected partners.

Our results show that delay in ART initiation was common among East African HIV-infected individuals in serodiscordant partnerships initiating ART for their own health, despite regular clinical and immunological monitoring, ART counseling, and active linkage into care. Positively, they emphasize some HIV-infected partners with higher CD4 counts may be interested in early ART for HIV prevention, particularly if they wish to conceive.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEGEMENTS

I thank the members of my committee (Drs. Jared Baeten, Connie Celum and Carey Farquhar) for their guidance and support. I am indebted to the thousands of Partners PrEP Study participants for their participation and contribution to this data resource. I thank the study sites clinicians Nyawira Gitahi-Kamau, Scovia Khakhasa, Rita Makabayi Mugabe, Betty Meli, Agnes Nakyanzi, Emmanuel Ocamaare, Edna Tindimwebwa, Imeldah Wakhungu, and Helen Wanja for their contributions to data collection. Thanks to Justin Brantley of the Department of Global Health at the University of Washington for programming assistance. Finally, I thank my Chair, Dr. Jared Baeten, for his outstanding mentorship, without which this work would not have been possible.

These studies were supported through research grants from the US National Institutes of Health (R01 MH095507) and the Bill & Melinda Gates Foundation (grant OPP47674). I am grateful to the International AIDS Research and Training Program (grant # D43 TW000007), Fogarty International Center of the National Institutes of Health for fellowship support.

DEDICATION

To my “pink world”:

To my great grandmother Kezia Babisherekamu (1879-1993), grandmother Huldah Kasabiiti Nyakatukura (1912-2013), and mother Lucy Nyangoma Karani (1935-2003) for a Godly heritage

To my family, Lindi, Lucy and Lisa whose love and support keep me going

To my parents, Peter and Perpetua Karani,

and my siblings Valerie, Linnet, Sarah and Simon,

I am because you are

Chapter 1

Delay of Antiretroviral Therapy Initiation is Common in East African HIV-Infected Individuals in Serodiscordant Partnerships

Summary

Introduction**:** For HIV-infected persons, initiation of antiretroviral therapy (ART) has important clinical and transmission benefits. Recent WHO guidance recommends ART initiation for persons with a known uninfected partner, as a strategy to prevent HIV transmission.

Methods**:** Among HIV-infected persons from Kenya and Uganda who had a known heterosexual HIV-uninfected partner, and were enrolled in the Partners PrEP Study, an HIV prevention clinical trial, we assessed ART initiation in those who became ART-eligible under national guidelines. HIV-infected partners received quarterly clinical and semi-annual CD4 monitoring, and active referral for ART upon becoming eligible.

Results**:** Of 1998 HIV-infected ART-eligible partners (58% women), the median age was 34 years (interquartile range [IQR] 28, 40). At first visit when determined to be ART eligible, the median CD4 count was 273 cells/μL (IQR 221, 328), 79% had WHO stage 1 or 2 HIV disease, and 96% were receiving trimethoprim-sulfamethoxazole prophylaxis. The cumulative probabilities of initiating ART at 6, 12, and 24 months after referral were 60.8%, 78.8% and 91.5%, respectively. Higher CD4 count (adjusted hazard ratio [AHR] 3.41, $p<0.001$ for 251-350 and AHR 6.23, $p<0.001$ for >350, compared with <200 cells/μL), asymptomatic HIV disease (AHR 1.52, $p=0.04$), and alcohol use (AHR 1.54, $p=0.001$) were independent predictors for delay in ART initiation.

Conclusions: In the context of close CD4 monitoring, ART counseling, and active linkage to HIV care, a substantial proportion of HIV-infected persons with a known HIV-uninfected partner delayed ART

initiation. Strategies to motivate ART initiation are needed, particularly for asymptomatic persons with higher CD4 counts.

Introduction

The past decade has seen significant progress in scaling up access to antiretroviral therapy (ART) in sub-Saharan Africa, and the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that in 2010 the proportion of ART-eligible persons on treatment in sub-Saharan Africa was 49%, an increase of 47% since 2003 (1, 2). Recent guidance from the World Health Organization (WHO) recommends immediate ART initiation, at any CD4 count, for HIV-infected individuals in HIV serodiscordant partnerships (3), to prevent HIV disease progression and transmission to uninfected partners (4). Implementing ART regardless of CD4 count for HIV serodiscordant partnerships will increase the number of ART-eligible persons in settings in which there is already considerable attrition in the continuum from HIV diagnosis to linkage to care and retention in treatment (5, 6).

Some HIV-infected individuals do not enroll in pre-ART care or decline treatment even when it is available. Studies from a variety of African settings have found that personal and provider barriers to ART initiation, including stigma and denial of need for ART, lack of symptoms (which could decrease motivation to initiate life-long therapy), fear of ART side effects, transportation costs, lengthy pre-treatment processing, and lack of access to CD4 testing (7-10). Understanding factors associated with ART-eligible individuals delaying or declining treatment will inform how to improve retention in pre-ART care, reduce HIV incidence and morbidity, and help design strategies to motivate treatment initiation at higher CD4 thresholds, particularly as treatment guidelines evolve towards treating earlier in the course of disease.

We conducted a prospective study to explore factors related to delay in ART initiation among HIV-infected members of HIV serodiscordant couples. We sought to define factors associated with delay or decline of ART despite active counseling of ART benefits and access to ART services.

Methods

Population and procedures

We conducted a prospective study among HIV-infected partners enrolled in the Partners PrEP Study, a randomized clinical trial of daily oral antiretroviral pre-exposure prophylaxis (PrEP) to decrease HIV acquisition within HIV serodiscordant heterosexual couples (ClinicalTrials.gov NCT00557245) (11). Beginning in July 2008, 4747 heterosexual HIV serodiscordant couples from nine research sites in Kenya and Uganda were enrolled and followed. HIV-uninfected partners were randomized to receive daily oral PrEP or placebo and followed for up to 36 months; in July 2011, the trial demonstrated efficacy of PrEP for HIV prevention and the use of placebo was discontinued.

For HIV-infected partners, study eligibility included CD4 cell count ≥250 cells/μL, no history of clinical AIDS-defining diagnoses, and not otherwise meeting national guidelines for ART initiation. Infected partners were followed quarterly in parallel with their uninfected partners and were monitored for HIV clinical status including semi-annual CD4 counts (12). Prior to initiation of the clinical trial, study sites were required to have established linkages with HIV care programs, and those affiliated with HIV care organizations reserved ART slots for study participants. The clinical trial protocol required that HIV-infected partners who became eligible during the study for initiation of ART according to the national guidelines of Kenya and Uganda be actively counseled to initiate treatment, referred, and linked into care. Specifically, participants were provided with a referral letter detailing clinical status and CD4 counts during the study and were linked to partnering HIV care programs through ongoing counseling, phone calls, and personal visits between clinical providers to limit barriers to ART initiation. Data about referral outcomes, and uptake of ART were recorded at quarterly study visits. During the trial, CD4 eligibility criteria for ART initiation in Kenya (<200 cells/μL) and Uganda (<250 cells/μL) were revised to ≤350 cells/μL in July 2010 and April 2012, respectively; WHO stage 3 or 4 HIV disease, if CD4 counts were ≥350 cells/μL was also a criterion for ART initiation in both countries.

Statistical analysis

The primary outcome was initiation of combination ART, not including short-course antiretroviral prophylaxis by pregnant women for the prevention of vertical transmission of HIV. Data on ART eligibility and initiation were obtained from structured questionnaires and entered into the trial database; ART use was assessed at each quarterly follow-up visit, with participants asked to report whether they were receiving ART. Dates of referral for ART and barriers to ART initiation reported during clinical and counseling sessions were abstracted from clinical charts onto a standardized abstraction form by one of the authors (AM). For those referred for ART initiation, follow-up time was counted from the date of referral. Participants who died, were lost to follow-up, or did not have a subsequent visit after ART referral were administratively censored at the last study visit. Those who had a subsequent visit, but who had not yet initiated ART were censored at their final follow-up visit; the study ended in December 2012. Participants who started ART >6 months (2 quarterly visits) after referral were considered to have delayed ART initiation. The cumulative probability of ART initiation was estimated using Kaplan-Meier methods. A Cox proportional hazards regression model was used to identify independent predictors of ART non-initiation; factors with p-values ≤0.10 in univariate analysis were included in a multivariate model. Statistical analyses were performed using Stata 12.1 (StataCorp, College Station, TX).

Ethical approval

The University of Washington Human Subjects Review Committee and ethics review committees at collaborating institutions at each of the study sites approved the study. All participants provided written informed consent.

Results

Population characteristics

Of the 4747 HIV-infected participants enrolled and followed in the Partners PrEP Study, 2184 (46%) became eligible for ART during study follow-up (Figure 1). Of these, 2178 were referred for initiation of ART, and 1998 (92%) had a subsequent study visit to assess ART uptake. For these 1998, the median age was 34 years (interquartile range [IQR] 28, 40), and 1163 (58%) were women (Table 1). Men were older than women [median age in years, 39 (IQR 34, 45) versus 30 (IQR 25, 35); Pearson Chi-square $p<0.001$)], and the median duration of partnership was 8 years (IQR 3, 14). For those who later came to meet ART eligibility guidelines, the median baseline CD4 count was 393 cells/μL (IQR 322, 495) and most (89%) had WHO stage 1 or 2 HIV disease at the time of study entry.

Initiation and Non-Initiation of Antiretroviral Therapy

At the time of ART eligibility, the median CD4 count was 273 cells/μL (IQR 221, 328): 299 (15%) had CD4 counts <200 cells/μL, 1457 (73%) had CD4 counts between 200 and 350 cells/μL, and 242 (12%) had CD4 counts >350 cells/μL with concurrent WHO stage 3 or 4 HIV disease. Most (96%) were on trimethoprim-sulfamethoxazole chemoprophylaxis. The median time from study enrollment to ART eligibility was 1.4 years (IQR 0.7, 1.9) and the median time from ART eligibility to referral was 2.1 months (IQR 0.5, 2.8). After referral, participants were followed for a median of 14 months (IQR 5, 21), and contributed 849 person-years of follow-up for the assessment of ART initiation.

Of the 1998 HIV-infected participants, 1422 (71.1%) initiated ART. The cumulative probabilities of initiating ART at 6, 12, and 24 months were 60.8%, 78.8% and 91.5%, respectively. For ART initiators, the median time from referral to starting ART was 2.9 months (IQR 2.3, 6.2). ART initiation differed according to CD4 cell count as measured at the time of referral. Overall, among those with CD4 counts <200 cells/μL, 87% started treatment (66% by 6 months) compared to 83% (69% by 6 months) of those with CD4 counts of 200-250 cells/μL, 63% (55% by 6 months) of those with CD4 counts between 251 and 350 cells/μL, and 55% (32% by 6 months) with CD4>350 cells/μL (log rank $p<0.001$) (Figure 2).

In multivariate analysis, higher CD4 count (adjusted hazard ratio [AHR] 3.41, p<0.001 for 251-350 cells/μL and AHR 6.23, p<0.001 for >350 cells/μL), asymptomatic HIV disease (AHR 1.52, p=0.04), and any alcohol use (AHR 1.54, p=0.001) predicted ART non-initiation (Table 2). Unprotected sex with the HIV-uninfected partner was not related to delay in ART initiation (p=0.4).

Of the 1998 participants who were referred for ART, chart notes were reviewed to assess spontaneously-reported barriers to ART initiation for 1593 (80%) (Table 3). Sixty-nine percent of ART initiators and 37% of non-initiators did not report specific impediments to starting treatment. For ART initiators, provider barriers included pre-treatment processing (10%) and repeat CD4 counts at the referral clinic which were greater than the ART eligibility threshold (6%); forty percent of ART non-initiators reported provider barriers (including pre-treatment counseling about ART, and high repeat CD4 counts) to ART initiation. Few (<5%) participants openly described stigma-related personal barriers as impediments to ART access.

Discussion

In this prospective study of East African ART-eligible HIV-infected persons with known HIV-uninfected partners, who received regular clinical and immunological monitoring, ART counseling, and active linkage to HIV care at partnering HIV clinics, ~40% of the treatment-eligible participants delayed ART initiation for more than 6 months after their initial referral for ART. Higher CD4 counts, asymptomatic HIV disease, and alcohol consumption were predictors of ART non-initiation. Provider barriers including several required pre-treatment eligibility assessment and counseling sessions, and repeat CD4 counts above the ART eligibility threshold, were commonly reported impediments to ART initiation.

The overall proportion of HIV-infected participants that initiated ART in our study is somewhat higher than in several studies from sub-Saharan Africa: in those studies, the overall proportion was 62.9% (13). Notably, the 6-month cumulative probability of ART initiation in our cohort is comparable to that reported in North America over the past decade (14). Regular counseling, clinical monitoring, and active linkage to HIV care in the context of a clinical trial likely motivated earlier start of ART in our population. Our finding that lower CD4 counts predict ART initiation is consistent with previous studies (15), perhaps because such HIV-infected persons are more motivated to start treatment, or are given priority by ART providers (16). Nevertheless, there was still considerable delay in our population of HIV-infected individuals in serodiscordant couples initiating ART for their own health.

We found that higher CD4 counts and asymptomatic HIV disease were associated with non-initiation of ART (17). Asymptomatic persons may be less motivated to commence life-long treatment, choosing instead to “live positively” (18). In a South African study, 37% of clients who declined ART cited feeling healthy as the reason not to commence treatment (19). Treatment providers may have been less likely to initiate ART in persons with higher CD4 counts, particularly during a period when Kenya and Uganda revised their ART initiation guidelines. Anecdotally, in this population, phone calls to remind clinicians at referral centers of updated national guidelines and WHO eligibility criteria (for those with CD4 counts >350 cells/μL) were sometimes employed. In view of recent WHO guidance to initiate ART in HIV-

infected members of serodiscordant couples regardless of CD4 count, counseling of ART-eligible persons, and training programs for providers, should emphasize the clinical and prevention benefits of earlier ART initiation, and address negative perceptions of treatment. Studies from other settings have found that alcohol abuse may be an impediment to initiating ART (20). ART providers in sub-Saharan Africa do not routinely screen for alcohol consumption despite the high burden of HIV and alcohol disease (21). Finding and treating HIV-infected individuals with alcohol dependence prior to ART initiation may improve treatment outcomes (22).

Pre-ART patient visits to assess willingness, readiness and ability to start ART were a common cause of delayed treatment initiation in our cohort. A recent study from Uganda found no benefit of additional visits before ART initiation on adherence or HIV RNA concentrations (23). In that study, participants who completed the three sessions for pre-ART counseling had significant delays from ART eligibility to initiation, compared with those who received counseling at the time of ART initiation. We also found that repeat CD4 counts above the ART eligibility threshold was a provider barrier to ART initiation, perhaps a result of physiologic intra-subject variability of CD4 counts (24) or assay performance at different laboratories. ART providers should recognize the intra-person and intra-laboratory variability in CD4 counts, and utilize trends of CD4 count decline and counts provided from referring providers, to avoid misclassifying persons as ART ineligible (25). Stigma, fear of disclosure and denial of the need to start treatment are important barriers to ART access (26), but may have been underreported in our cohort. Among Kenyan HIV serodiscordant couples, fear of ART side effects and stigma were common reasons for reluctance to initiate early ART (27, 28). Importantly, lack of treatment slots was not a significant barrier to ART initiation in our cohort. For known HIV serodiscordant couples, HIV prevention services, including PrEP as a bridge to ART, may be particularly important in HIV serodiscordant couples in which the HIV-infected partner declines or delays ART initiation.

The strengths of our study include the prospective design that permitted longitudinal follow-up of a large cohort of HIV-infected individuals, who received HIV primary care at quarterly visits and ascertainment of immunological and ART status. Our study has limitations. HIV-infected participants enrolled in a clinical

trial with regular counseling, clinical and laboratory monitoring may have been more intensive than what is generally implemented in many African settings. To understand barriers to ART initiation, we abstracted data from clinical charts, which relied on participants' self-reports and thus that subset of data are likely an underestimate of the range of barriers encountered.

In summary, among East African HIV-infected individuals eligible for ART and who had a known HIV-uninfected partner, about half did not initiate ART for at least 6 months. Future studies should evaluate strategies to motivate ART initiation, particularly for asymptomatic persons with higher CD4 counts, including HIV-infected members of serodiscordant couples.

Table 1. Characteristics of East African HIV-infected women and men with a known HIV-uninfected partner

Characteristic	All HIV-infected persons, at study enrollment (N=4747)	Subset who became ART-eligible and who had follow-up to assess ART uptake (N=1998)	
Age in years, median (IQR)	34 (28, 40)	34 (28, 40)	
18–24	828 (17)	258 (13)	
25–34	1922 (41)	804 (40)	
35-44	1443 (30)	660 (33)	
≥45	554 (12)	276 (14)	
Sex			
Women	2962 (62)	1163 (58)	
Men	1785 (38)	835 (42)	
		At enrollment N (%)	**At time of ART eligibility** N (%)
Median CD4 count in cells/μL, (IQR)	496 (375, 662)	393 (322, 495)	273 (221, 328)
<200	0 (0)	0 (0)	299 (15)
200-250	3 (<1%)	2 (<1%)	583 (30)
251-350	919 (19)	695 (35)	874 (43)
>350	3825 (81)	1301 (65)	242 (12)
WHO clinical stage			
1	3006 (63)	1132 (57)	796 (40)
2	1431 (30)	637 (32)	775 (39)
3	310 (7)	229 (12)	389 (19)
4	0 (0)	0 (0)	38 (2)

Trimethoprim-sulfamethoxazole prophylaxis			
Yes	3528 (74)	1476 (74)	1920 (96)
No	1219 (26)	522 (26)	78 (4)
Enrolled in HIV care program			
Yes	3256 (69)	1392 (70)	1734 (87)
No	1491 (31)	606 (30)	264 (13)

Table 2. Correlates of ART non-initiation in ART-eligible women and men

	Univariate models		Adjusted model	
Characteristic	**Hazard ratio (95% CI)**	**p-value**	**Adjusted hazard ratio (95% CI)**	**p-value**
Demographic Characteristics				
Age (years)*				
≥40	Referent		Referent	
30-39	1.23 (0.96, 1.57)	0.10	1.16 (0.87, 1.48)	0.36
<30	1.27 (0.98, 1.64)	0.07	1.15 (0.89, 1.47)	0.29
Sex				
Women	Referent			
Men	1.09 (0.90, 1.32)	0.40		
Education, (years)*				
≤7	Referent			
>7	0.88 (0.73, 1.06)	0.19		
Monthly income*				
None	Referent			
Any	1.02 (0.84, 1.23)	0.87		
Alcohol consumption*				
None	Referent		Referent	
Any	1.27 (0.99, 1.62)	0.05	1.54 (1.20, 1.98)	0.001
Children with partner*				
None	Referent			
Any	0.98 (0.79, 1.23)	0.89		
Duration of known serodiscordant status*				
≥1 year	Referent			

<1 year	0.85 (0.69, 1.04)	0.12		
Unprotected sex with study partner**				
None	Referent			
Any	1.11 (0.85, 1.47)	0.44		
Clinical Characteristics				
CD4 count (cells/μL)**				
<200	Referent		Referent	
200-250	1.43 (0.93, 2.20)	0.11	1.41 (0.92, 2.18)	0.12
251-350	3.30 (2.22, 4.88)	<0.001	3.41 (2.30, 5.06)	<0.001
>350	4.14 (2.68, 6.40)	<0.001	6.23 (3.53, 10.99)	<0.001
WHO clinical stage**				
3 or 4	Referent		Referent	
1 or 2	0.83 (0.67, 1.03)	0.10	1.52 (1.02, 2.26)	0.04

Footnotes to Table 2

*At Baseline

**At the time of ART eligibility

Table 3. Reported barriers to ART initiation, as documented in participant chart notes

	Initiated ART (n=1144) N (%)	Did not initiate ART (n=449) N (%)
No barriers	786 (69)	166 (37)
Provider barriers		
Required pre-treatment counseling sessions	119 (10)	77 (17)
Repeat CD4 count at clinic greater than eligibility threshold	69 (6)	83 (18)
WHO stage not considered and ART not prescribed	05 (<1)	12 (3)
No ART slots	27 (2)	07 (2)
Personal barriers		
Did not go to referral facility	60 (5)	44 (10)
Stigma	14 (1)	16 (4)
Not ready to start ART	14 (1)	15 (3)
Declined referral	12 (1)	08 (2)
Fear of ART side effects	17 (1)	05 (1)
Feels healthy	16 (1)	06 (1)
Other	05 (<1)	10 (2)

Figure 1. Follow-up of East African HIV-infected women and men

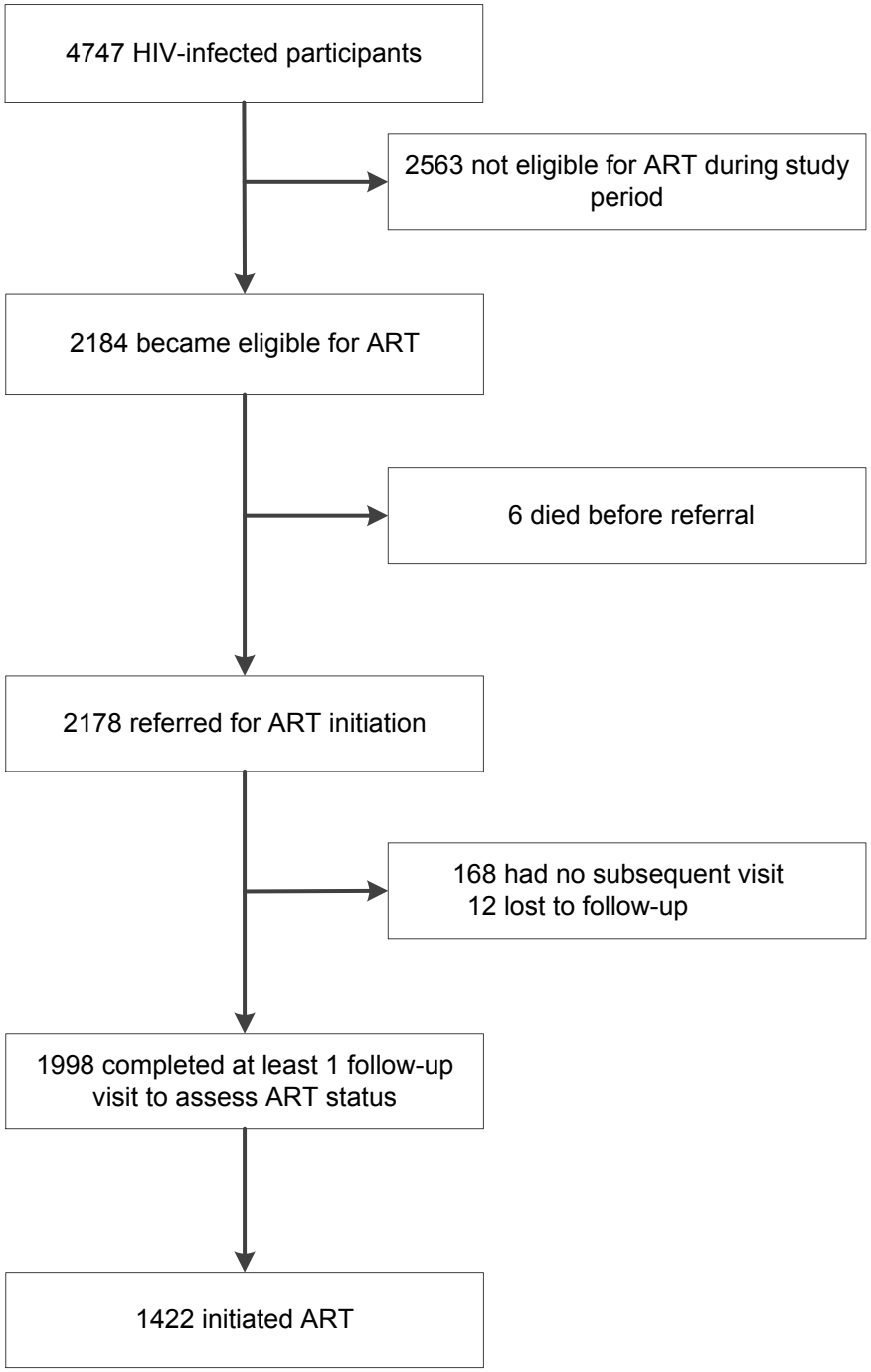
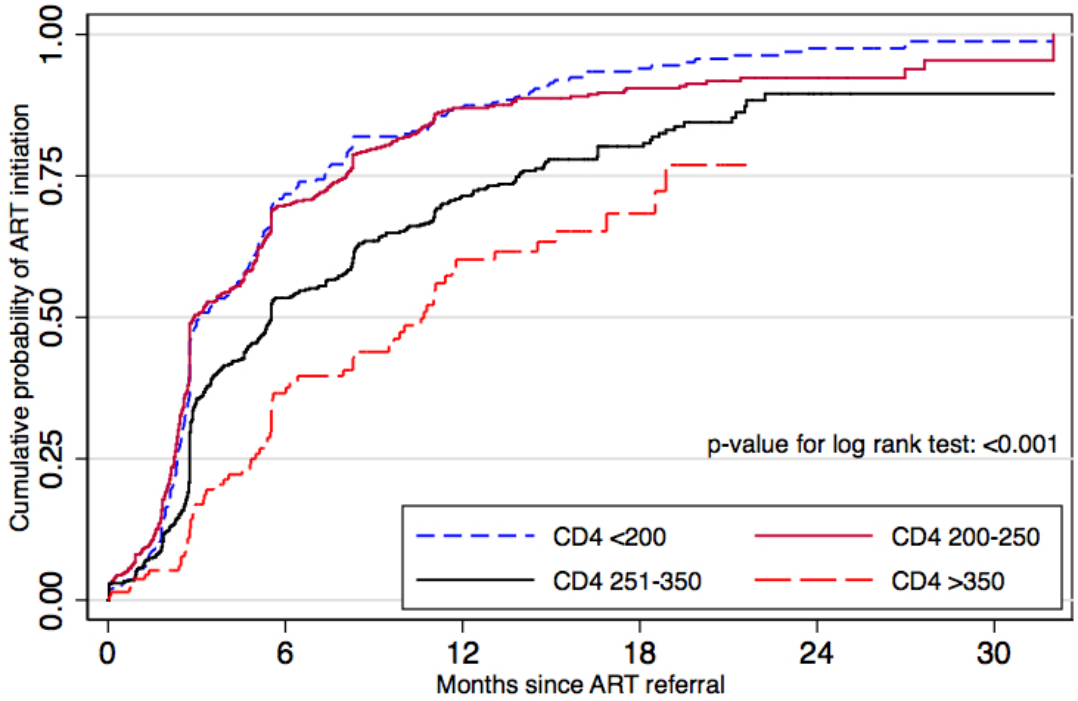


Figure 2. Cumulative probability of ART initiation, by CD4 count at the time of ART eligibility and referral



Number at risk

<200	258	65	28	11	4	1
200-250	506	137	48	25	9	3
251-350	669	223	99	35	4	1
>350	148	63	28	9	0	0

Notes to Chapter 1

1. WHO, UNAIDS, UNICEF. Towards Universal Access: Scaling up priority HIV/AIDS Interventions in the Health Sector. 2011: Available from: http://www.who.int/hiv/pub/progress_report2011/summary_en.pdf.

2. WHO. Treat 3 Million by 2005 Initiative. 2003 [cited 2013 May 5]: Available from: http://www.who.int/3by5/publications/documents/en/3by5StrategyMakingItHappen.pdf.

3. WHO. Guidance on couples HIV testing and counselling, including antiretroviral therapy for treatment and prevention in serodiscordant couples: Recommendations for a public health approach. 2012 [cited 2012 August 16]; Available from: http://www.who.int/hiv/pub/guidelines/9789241501972/en/.

4. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011 Aug 11;365(6):493-505.

5. Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. PLoS Med. 2011 Jul;8(7):e1001056.

6. Clouse K, Pettifor AE, Maskew M, Bassett J, Van Rie A, Behets F, et al. Patient Retention From HIV Diagnosis Through One Year on Antiretroviral Therapy at a Primary Health Care Clinic in Johannesburg, South Africa. J Acquir Immune Defic Syndr. 2013 Feb 1;62(2):e39-e46.

7. McGrath N, Glynn JR, Saul J, Kranzer K, Jahn A, Mwaungulu F, et al. What happens to ART-eligible patients who do not start ART? Dropout between screening and ART initiation: a cohort study in Karonga, Malawi. BMC Public Health. 2010;10:601.

8. Micek MA, Gimbel-Sherr K, Baptista AJ, Matediana E, Montoya P, Pfeiffer J, et al. Loss to follow-up of adults in public HIV care systems in central Mozambique: identifying obstacles to treatment. J Acquir Immune Defic Syndr. 2009 Nov 1;52(3):397-405.

9. Losina E, Bassett IV, Giddy J, Chetty S, Regan S, Walensky RP, et al. The "ART" of linkage: pre-treatment loss to care after HIV diagnosis at two PEPFAR sites in Durban, South Africa. PLoS One. 2010;5(3):e9538.

10. Geng EH, Bangsberg DR, Musinguzi N, Emenyonu N, Bwana MB, Yiannoutsos CT, et al. Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach. J Acquir Immune Defic Syndr. 2010 Mar;53(3):405-11.

11. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012 Aug 2;367(5):399-410.

12. Mujugira A, Baeten JM, Donnell D, Ndase P, Mugo NR, Barnes L, et al. Characteristics of HIV-1 Serodiscordant Couples Enrolled in a Clinical Trial of Antiretroviral Pre-Exposure Prophylaxis for HIV-1 Prevention. PLoS One. 2011;6(10):e25828.

13. Mugglin C, Estill J, Wandeler G, Bender N, Egger M, Gsponer T, et al. Loss to programme between HIV diagnosis and initiation of antiretroviral therapy in sub-Saharan Africa: systematic review and meta-analysis. Trop Med Int Health. 2012 Sep 20.

14. Hanna DB, Buchacz K, Gebo KA, Hessol NA, Horberg MA, Jacobson LP, et al. Trends and Disparities in Antiretroviral Therapy Initiation and Virologic Suppression Among Newly Treatment-

Eligible HIV-Infected Individuals in North America, 2001-2009. Clin Infect Dis. 2013 Apr;56(8):1174-82.

15. Bassett IV, Wang B, Chetty S, Mazibuko M, Bearnot B, Giddy J, et al. Loss to care and death before antiretroviral therapy in Durban, South Africa. J Acquir Immune Defic Syndr. 2009 Jun 1;51(2):135-9.

16. Parkes-Ratanshi R, Bufumbo L, Nyanzi-Wakholi B, Levin J, Grosskurth H, Lalloo DG, et al. Barriers to starting ART and how they can be overcome: individual and operational factors associated with early and late start of treatment. Trop Med Int Health. [Research Support, Non-U.S. Gov't]. 2010 Nov;15(11):1347-56.

17. Fleishman JA, Yehia BR, Moore RD, Gebo KA, Agwu AL. Disparities in receipt of antiretroviral therapy among HIV-infected adults (2002-2008). Med Care. 2012 May;50(5):419-27.

18. Opadina F. Living positively with HIV. Afr Health. 1995 Mar;17(3):35.

19. Katz IT, Essien T, Marinda ET, Gray GE, Bangsberg DR, Martinson NA, et al. Antiretroviral Refusal among Newly Diagnosed HIV-Infected Adults in Soweto, South Africa. AIDS. 2011 Aug 9.

20. Tegger MK, Crane HM, Tapia KA, Uldall KK, Holte SE, Kitahata MM. The effect of mental illness, substance use, and treatment for depression on the initiation of highly active antiretroviral therapy among HIV-infected individuals. AIDS Patient Care STDS. 2008 Mar;22(3):233-43.

21. Chersich MF, Rees HV, Scorgie F, Martin G. Enhancing global control of alcohol to reduce unsafe sex and HIV in sub-Saharan Africa. Global Health. 2009;5:16.

22. Neblett RC, Hutton HE, Lau B, McCaul ME, Moore RD, Chander G. Alcohol consumption among HIV-infected women: impact on time to antiretroviral therapy and survival. J Womens Health (Larchmt). 2011 Feb;20(2):279-86.

23. Siedner MJ, Lankowski A, Haberer JE, Kembabazi A, Emenyonu N, Tsai AC, et al. Rethinking the "pre" in pre-therapy counseling: no benefit of additional visits prior to therapy on adherence or viremia in Ugandans initiating ARVs. PLoS One. 2012;7(6):e39894.

24. Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from human immunodeficiency virus type 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr. 1990;3(2):144-51.

25. Guthrie BL, Choi RY, Liu AY, Mackelprang RD, Rositch AF, Bosire R, et al. Barriers to Antiretroviral Initiation in HIV-1-Discordant Couples. Journal of acquired immune deficiency syndromes. 2011 Aug 4.

26. Fox MP, Mazimba A, Seidenberg P, Crooks D, Sikateyo B, Rosen S. Barriers to initiation of antiretroviral treatment in rural and urban areas of Zambia: a cross-sectional study of cost, stigma, and perceptions about ART. J Int AIDS Soc. 2010;13:8.

27. Heffron R, Ngure K, Mugo N, Celum C, Kurth A, Curran K, et al. Willingness of Kenyan HIV-1 serodiscordant couples to use antiretroviral based HIV-1 prevention strategies. J Acquir Immune Defic Syndr. 2012 May 16.

28. Kahn TR, Desmond M, Rao D, Marx GE, Guthrie BL, Bosire R, et al. Delayed initiation of antiretroviral therapy among HIV-discordant couples in Kenya. AIDS Care. 2013;25(3):265-72.

Chapter 2

Fertility Intentions and Interest in Early Antiretroviral Therapy among East African HIV-Infected Individuals in Serodiscordant Partnerships

Summary

Background**:** Early antiretroviral therapy (ART) (i.e., at CD4 counts >350 cells/μL) reduces HIV transmission risk within HIV serodiscordant couples. Couples often desire children and risk HIV transmission in order to conceive. We investigated fertility intentions and interest in early ART for HIV prevention among HIV-infected East Africans in mutually-disclosed, heterosexual HIV serodiscordant partnerships.

Methods**:** Between July and December 2011, we conducted a cross-sectional study among 1051 HIV serodiscordant couples participating in the Partners PrEP Study of antiretroviral pre-exposure prophylaxis (PrEP) for HIV prevention in Kenya and Uganda. We analyzed couples with intact serodiscordant partnerships, in which the HIV-infected partners had CD4 counts >350 cells/μL, did not have WHO stage 3 or 4 HIV disease, and were not already on ART. We used descriptive methods and multivariate logistic regression to determine whether fertility intentions were correlated with a greater likelihood to use early ART for prevention.

Results**:** Of 571 HIV serodiscordant couples who met study criteria and were included in this analysis, 368 (64%) were couples with HIV-infected female partners. For HIV-infected partners, the median age was 34 years (interquartile range [IQR] 28-40), and the median CD4 count was 586 cells/μL (IQR 461, 765). Most (76% and 71% of men and women, respectively) indicated willingness to start early ART, and 33% expressed fertility intentions. HIV-infected partners desiring children were significantly more likely to express interest in early ART (adjusted odds ratio [aOR] 1.83, p=0.02) than those without fertility desires. Age ≤24 years (aOR 10.63, p<0.001), male gender (aOR 1.65, p=0.05), lack of children with the partner

(aOR 2.53, p=0.002), and unprotected sex in the prior month (aOR 1.67, p=0.05) were also associated with fertility intentions.

Conclusions**:** East African HIV serodiscordant couples desiring children were nearly twice as interested in early ART for HIV prevention as HIV serodiscordant couples not desiring children. Early ART would reduce the risk of both sexual transmission of HIV as well as mother-to-child HIV transmission. Couples who desire children are a priority population for implementing early ART for HIV prevention.

J Acquir Immune Defic Syndr. Volume 63, Number 1, May 1, 2013

Introduction

In sub-Saharan Africa, stable, heterosexual HIV serodiscordant couples (i.e., one member is HIV-infected and the other uninfected) account for a substantial proportion of new infections and are a priority population for novel prevention interventions (1). Serodiscordant couples frequently have high pregnancy incidence and intentionally risk HIV transmission in order to conceive (2, 3). Earlier antiretroviral therapy (ART) initiation (i.e., at CD4 counts >350 cells/μL) substantially reduces the risk of HIV transmission within HIV serodiscordant couples (4). Early ART may reduce peri-conception HIV transmission risk due to decreased HIV viral load and infectiousness (5, 6). We investigated fertility intentions and interest in early ART for HIV prevention among East African HIV-infected individuals in serodiscordant partnerships.

Methods

Between July and December 2011, we conducted a cross-sectional study among Kenyan and Ugandan heterosexual HIV serodiscordant couples participating in the Partners PrEP Study, a phase III, multisite, randomized, placebo-controlled trial of oral pre-exposure prophylaxis (PrEP) for HIV prevention (7). During the trial, participants received standard HIV prevention services including regular HIV risk-reduction counseling and free condoms. They were informed and counseled about the results of clinical trials of new interventions for HIV prevention, including HPTN 052 and the clinical and prevention benefits of early ART (4, 8). In July 2011, the independent data and safety monitoring board recommended that the placebo arm of the trial be discontinued due to clear demonstration of PrEP efficacy for HIV prevention (8). Unblinding visits were conducted at which the results of the study were conveyed. HIV uninfected partners in the placebo arm were thereafter offered active PrEP. Standardized questionnaires were administered regarding partnership status, willingness to have the HIV-infected partner start ART at CD4 counts >350 cells/μL if it would lower risk of transmitting HIV to their partner, perceived benefits and concerns about early ART, and the number and timing of additional children.

For this analysis, data were analyzed from couples in which the HIV-infected participants had CD4 counts >350 cells/μL and did not have WHO stage 3 or 4 HIV disease (i.e., did not meet criteria for initiation of ART under WHO guidelines at the time), were not already on ART, and whose serodiscordant partnership was intact. We used descriptive analytical methods and multivariate logistic regression models to evaluate the association between fertility intentions and interest in early ART after adjusting for *a priori* confounders (age, sex, education, partnership duration, number of children, coital frequency, unprotected sex and contraception). Data were analyzed using Stata 12.1 (StataCorp, College Station, TX). The University of Washington Human Subjects Review Committee and ethics review committees at collaborating institutions at each of the study sites approved the study procedures. All participants provided written informed consent.

Results

A total of 571 HIV serodiscordant couples completed the questionnaire and were included in the analysis, of which 368 (64%) were couples in which the HIV-infected partner was female. For HIV-infected partners, the median age was 34 years (interquartile range [IQR] 28, 40), and the median CD4 cell count was 586 cells/μL (IQR 461, 765). Couples had a median duration of partnership of 8.3 years (IQR 3.6, 14.8), and a median of 2 children (IQR 1, 4).

Fertility intentions were common, expressed by 36% of HIV-infected women and 28% of HIV-infected men. For the majority of couples (76%), HIV-uninfected partners were in agreement with the fertility intentions of their HIV-infected partners: for 314 couples (55%), both members did not want more children, whereas for 121 couples (21%), both members desired additional children. One hundred thirty-six couples (24%) had discordant fertility intentions, the majority of which (74%) were couples in which the HIV-uninfected male partner desired additional children but their HIV-infected female partner did not.

A majority of the 571 HIV-infected participants with CD4>350 cells/μL indicated willingness to start early ART for HIV prevention: 76% and 71% of men and women. HIV-infected partners with fertility intentions were significantly more likely to express interest in early ART for HIV prevention (adjusted odds ratio [aOR] 1.83, 95% confidence interval [CI], 1.12-2.99, p=0.02) than those without fertility intentions. Younger age (<25 years), male sex, lack of children with their partner, and unprotected sex in the prior month were also associated with fertility intentions among the HIV-infected partners (Table 1).

Discussion

In summary, fertility intentions were common and interest in early ART for HIV prevention was high among East African HIV-infected individuals in heterosexual, mutually-disclosed serodiscordant partnerships. All couples had received counseling about the efficacy of ART for HIV prevention, and those who desired to have children were nearly twice as likely to express interest in early ART as those without fertility intentions.

Our finding that HIV-infected individuals with fertility intentions were more likely to report unprotected sex is consistent with other studies from sub-Saharan Africa (2, 9), and reflects the need for safer conception counseling and services for HIV serodiscordant couples. Our findings suggest that both men and women in HIV serodiscordant partnerships desire children, with somewhat higher interest for men, possibly reflecting desire to have biologic children with a current partner, the perception of fertility as proof of virility, or sociocultural pressures (10, 11).

The World Health Organization (WHO) has recently recommended early ART for HIV-infected members of serodiscordant couples to reduce risk of HIV transmission to uninfected partners (12). Our results emphasize that a majority of HIV-infected persons with higher CD4 counts may be interested in early ART, particularly those who desire to conceive. Future studies should explore the feasibility and acceptability of implementing early ART for HIV prevention in African HIV serodiscordant couples desiring children.

Notes to Chapter 2

1. Coburn BJ, Gerberry DJ, Blower S. Quantification of the role of discordant couples in driving incidence of HIV in sub-Saharan Africa. Lancet Infect Dis. 2011 Apr;11(4):263-4.

2. Ngure K, Mugo N, Celum C, Baeten JM, Morris M, Olungah O, et al. A qualitative study of barriers to consistent condom use among HIV-1 serodiscordant couples in Kenya. AIDS Care. 2012;24(4):509-16.

3. Mugo NR, Heffron R, Donnell D, Wald A, Were EO, Rees H, et al. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples. AIDS. 2011 Sep 24;25(15):1887-95.

4. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011 Aug 11;365(6):493-505.

5. Mastro TD, Cohen MS, Rees H. Antiretrovirals for safer conception for HIV-negative women and their HIV-1-infected male partners: how safe and how available? AIDS. 2011 Oct 23;25(16):2049-51.

6. Vernazza PL, Graf I, Sonnenberg-Schwan U, Geit M, Meurer A. Preexposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child. AIDS. 2011 Oct 23;25(16):2005-8.

7. Mujugira A, Baeten JM, Donnell D, Ndase P, Mugo NR, Barnes L, et al. Characteristics of HIV-1 Serodiscordant Couples Enrolled in a Clinical Trial of Antiretroviral Pre-Exposure Prophylaxis for HIV-1 Prevention. PLoS One. 2011;6(10):e25828.

8. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012 Aug 2;367(5):399-410.

9. Bunnell R, Opio A, Musinguzi J, Kirungi W, Ekwaru P, Mishra V, et al. HIV transmission risk behavior among HIV-infected adults in Uganda: results of a nationally representative survey. AIDS. 2008 Mar 12;22(5):617-24.

10. Cooper D, Moodley J, Zweigenthal V, Bekker LG, Shah I, Myer L. Fertility intentions and reproductive health care needs of people living with HIV in Cape Town, South Africa: implications for integrating reproductive health and HIV care services. AIDS Behav. 2009 Jun;13 Suppl 1:38-46.

11. Cooper D, Harries J, Myer L, Orner P, Bracken H, Zweigenthal V. "Life is still going on": reproductive intentions among HIV-positive women and men in South Africa. Soc Sci Med. 2007 Jul;65(2):274-83.

12. WHO. Guidance on couples HIV testing and counselling, including antiretroviral therapy for treatment and prevention in serodiscordant couples: Recommendations for a public health approach. 2012 [cited 2012 August 16];
Available from: http://www.who.int/hiv/pub/guidelines/9789241501972/en/

Table 4: Correlates of Fertility Intentions Among East African HIV-Infected Women and Men

Factor	Fertility Intentions		Risk Estimates	
	Yes (N=190)	No (N=381)	Adjusted OR (95% CI)	p-value
Interest in early ART [a]				
No	45 (29)	108 (71)	Ref	
Yes	145 (35)	273 (65)	1.83 (1.12, 2.99)	0.02
Age (years)				
≥45	8 (12)	58 (88)	Ref	
35-44	33 (19)	144 (81)	1.68 (0.67, 4.22)	0.3
25-34	88 (39)	137 (61)	4.97 (1.96, 12.63)	<0.001
18-24	61 (59)	42 (41)	10.63 (3.68, 30.70)	<0.001
Sex				
Women	134 (36)	234 (64)	Ref	
Men	56 (28)	147 (72)	1.65 (1.00, 2.73)	0.05
Education (years)				
None	18 (31)	40 (69)	Ref	
Primary	120 (32)	251 (68)	0.87 (0.43, 1.76)	0.7
Secondary	52 (37)	90 (63)	0.98 (0.45, 2.14)	0.9
Partnership duration (years)				
≤5	97 (50)	97 (50)	Ref	
6-10	47 (35)	89 (65)	0.76 (0.43, 1.76)	0.3
11-37	42 (18)	181 (81)	0.67 (0.45, 2.14)	0.2
Children with partner				
Any	136 (29)	338 (71)	Ref	
None	54 (56)	43 (44)	2.54 (1.42, 4.53)	0.002
Unprotected sex, prior month				
None	126 (32)	272 (68)	Ref	
Any	46 (46)	54 (54)	1.67 (1.00, 2.77)	0.05

Footnote to Table 4: [a] ART = antiretroviral therapy