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

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Abstract

Objective—WHO guidance recommends antiretroviral therapy (ART) initiation for all persons with a known HIV-uninfected partner, as a strategy to prevent HIV transmission. Uptake of ART among HIV-infected partners in serodiscordant partnerships is not known, which we evaluated in African HIV serodiscordant couples.

Design—Prospective cohort study.

Methods—Among HIV-infected persons from Kenya and Uganda who had a known heterosexual HIV-uninfected partner, we assessed ART initiation in those who became ART-eligible under national guidelines during follow-up. Participants received quarterly clinical and semi-annual CD4 monitoring, and active referral for ART upon becoming eligible.

Results—Of 1958 HIV-infected ART-eligible partners, 58% were women and the median age was 34 years. At the first visit when determined to be ART eligible, the median CD4 count was 273 cells/μL (IQR 221, 330), 77% 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 eligibility were 49.9%, 70.0% and 87.6%, respectively. Younger age (<25

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Conflicts of Interest
The authors report no conflicts of interest.

Author contributions
AM, CC, and JMB designed the study. AM and JMB wrote the first draft. AM performed the statistical analyses. All authors contributed to data collection, interpretation of the results and the writing of the manuscript, and all approved the final draft.

Competing interests
The authors report no competing interests.

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years) (adjusted hazard ratio [AHR] 1.39, p=0.001), higher CD4 count (AHR 1.95, p<0.001 for >350 compared with <200 cells/μL), higher education (AHR 1.25, p<0.001), and lack of income (AHR 1.15, p=0.02) 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 younger persons with higher CD4 counts.

Keywords

HIV; CD4; Linkage to care; Antiretroviral therapy; Africa

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 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 ART even when it is available at no cost. Studies from a variety of African settings have found that personal and provider barriers to ART initiation include 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-associated morbidity, and help design strategies to motivate treatment initiation at higher CD4 counts, 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 about ART benefits, provision of referrals to HIV clinics, 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 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 initiation and use of ART were recorded at quarterly study visits using structured questionnaires. 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

For the present analysis, the primary outcome was initiation of combination ART among HIV-infected partners, not including short-course antiretroviral prophylaxis by pregnant women for the prevention of vertical transmission of HIV. Participants were included in the analysis if they became ART-eligible during study follow-up and had a subsequent visit at which ART uptake was assessed. Follow-up time was counted from the date of eligibility to report of ART, or for those who had not yet initiated ART at the time of their last visit, to date of last attended visit. The study ended in December 2012.

In a sensitivity analysis, follow-up from the time of referral for ART initiation, rather than ART eligibility was considered. Dates of referral for ART were not recorded in the study database but were instead collected in chart notes at the study site. At the end of the study, one of the authors (AM) abstracted referral dates and barriers to ART initiation reported during clinical and counseling sessions from clinical charts onto a standardized abstraction form. The sensitivity analysis was limited to ART-eligible HIV-infected participants who had documented dates of referral for ART, and follow-up time was counted from the date of referral.

For the primary and sensitivity analyses, the cumulative probability of ART initiation was estimated using Kaplan-Meier methods. Cox proportional hazards regression models were

used to identify independent predictors of ART non-initiation; factors with p-values ≤0.10 in univariate analysis were included in multivariate models. 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, of which 1958 (90%) were included in the present analysis (Figure 1). For these 1958, the median age was 34 years (interquartile range [IQR] 28, 40), and 1130 (58%) were women (Table 1). Men were older than women [median age in years, 39 (IQR 34, 44) versus 30 (IQR 25, 35), p<0.001)], and the median duration of partnership was 8 years (IQR 3, 14). The median baseline CD4 count was 391 cells/μL (IQR 320, 492) and most (87%) 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, 330): 292 (15%) had CD4 counts <200 cells/μL, 1410 (72%) had CD4 counts between 200 and 350 cells/μL, and 256 (13%) 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, 1.8). After becoming ART-eligible, participants were followed for a median of 1.4 years (IQR 0.5, 1.9), contributing a total of 1236 person-years of follow-up for the assessment of ART initiation.

Of the 1958 HIV-infected participants with follow-up, 1431 (73.1%) initiated ART. The cumulative probabilities of initiating ART at 6, 12, and 24 months were 49.9%, 70.0% and 87.6%, respectively. For those initiating ART, the median time from eligibility to starting ART was 5.5 months (IQR 2.8, 8.3). The likelihood of ART initiation differed according to CD4 cell count at the time of eligibility (Figure 2), with higher cumulative probabilities of ART initiation at 6 and 12 months for those with lower CD4 counts: among those with CD4 counts <200 cells/μL, 63% and 83%, compared to 59% and 80% for those with CD4 counts of 200–250 cells/μL, 43% and 63% for those with CD4 counts between 251 and 350 cells/μL, and 33% and 48% for those with CD4 counts >350 cells/μL (log rank p<0.001).

In multivariate analysis, age <25 years (adjusted hazard ratio [AHR] 1.39, p=0.001), higher education (AHR 1.25, p<0.001), lack of income (AHR 1.15, p=0.02), and higher CD4 count (AHR 1.43, p<0.001 for 251–350 cells/μL and AHR 1.95, p<0.001 for >350 cells/μL) predicted ART non-initiation (Table 2). Gender, alcohol consumption, and unprotected sex with the HIV-uninfected partner were not related to delay in ART initiation.

In sensitivity analyses restricted to HIV-infected participants for whom referral dates were available (N=1642), the median time from ART eligibility to referral was 2.7 months (IQR 0.5, 2.8) and the median time from referral to ART initiation was 3.2 months (IQR 2.4, 7.2). The cumulative probabilities of ART initiation at 6, 12, and 24 months from the time of referral were 56.8%, 75.5% and 89.4%, respectively. Similar to the primary analysis using time from ART eligibility, younger age, higher education, lack of income, and higher CD4 count were significantly associated in multivariate analysis with delay in ART initiation when time from ART referral was used (data not shown).

Of the 1642 participants for whom the precise timing of referral for ART could be abstracted, chart notes were further reviewed to assess spontaneously-reported barriers to ART initiation for 1568 (96%) (Table 3). Sixty-eight percent of ART initiators and 39% 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%); 41% of ART non-initiators reported provider barriers (including pre-treatment counseling about ART [18%], and high repeat CD4 counts [18%]) 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, all received regular clinical and immunological monitoring, ART counseling, and active linkage to HIV care at partnering HIV clinics, and half of the treatment-eligible participants delayed ART initiation for more than six months after becoming eligible for ART. Younger age, higher education, lack of income, and higher CD4 counts 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 cumulative 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 approximate 50% 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 start of ART in our population. Our finding that lower CD4 counts predicted sooner ART initiation is consistent with previous studies [15], perhaps because HIV-infected persons with known lower CD4 counts may be more motivated to start treatment, are given priority by ART providers, or more strongly encouraged to start ART by 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 younger age and higher CD4 counts were associated with non-initiation of ART [17]. Asymptomatic younger 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 the period when revised ART initiation guidelines (increasing the threshold from 200–250 to 350 cells/μL) were being implemented in Kenya and Uganda. Anecdotally, phone calls to referral centers were sometimes employed to remind referral clinicians of updated national guidelines. 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 lack of income, particularly as it relates to transport costs, is an economic barrier to ART initiation [20]. Although we provided transport re-imbursements for study visits, participants may have had difficulty accessing ART from other providers. We found that higher education was associated with ART non-initiation; the reasons for delayed ART initiation related to education are unknown but may relate to a more nuanced understanding of CD4 thresholds for starting treatment, and thus requests for repeat CD4 counts prior to accepting referrals, employment demands, or other factors.

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 [22]. 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 clinics repeated CD4 counts, which when above the ART eligibility threshold, was a provider barrier to ART initiation; the variability in CD4 test results could be due to physiologic intra-subject variability of CD4 counts [23] or assay performance between laboratories, and counseling about the difference in CD4 counts and the need for a subsequent CD4 test to verify ART eligibility could confuse patients, and lead to a substantial delay in ART initiation. 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 [24]. Stigma, fear of disclosure and denial of the need to start treatment are important barriers to ART access [25] but may be under-represented among mutually-disclosed clinical trial participants. Among Kenyan HIV serodiscordant couples, fear of ART side effects and stigma were common reasons for reluctance to initiate early ART [26, 27]. Importantly, lack of ART availability at referral centers was not a significant barrier to ART initiation in our cohort. For known HIV serodiscordant couples, HIV prevention services, including offering PrEP as a bridge until the HIV-infected partner initiates ART, may be particularly important in HIV serodiscordant couples in which the HIV-infected partner declines or delays ART initiation despite knowledge of the dual treatment and prevention benefits of ART and active linkage to HIV care.

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. These qualitative data may have underestimated the range of barriers encountered, but still provide valuable insight.

In summary, among East African HIV-infected individuals who were eligible for ART, had a known HIV-uninfected partner and were thus motivated to prevent HIV transmission, half did not initiate ART for at least 6 months indicating the importance of individual and structural barriers to ART. Future studies should evaluate strategies to address structural barriers to ART, such as repeat CD4 counts and multiple pre-ART eligibility visits, and to motivate ART initiation, particularly for young asymptomatic persons with higher CD4 counts, including HIV-infected members of serodiscordant couples.

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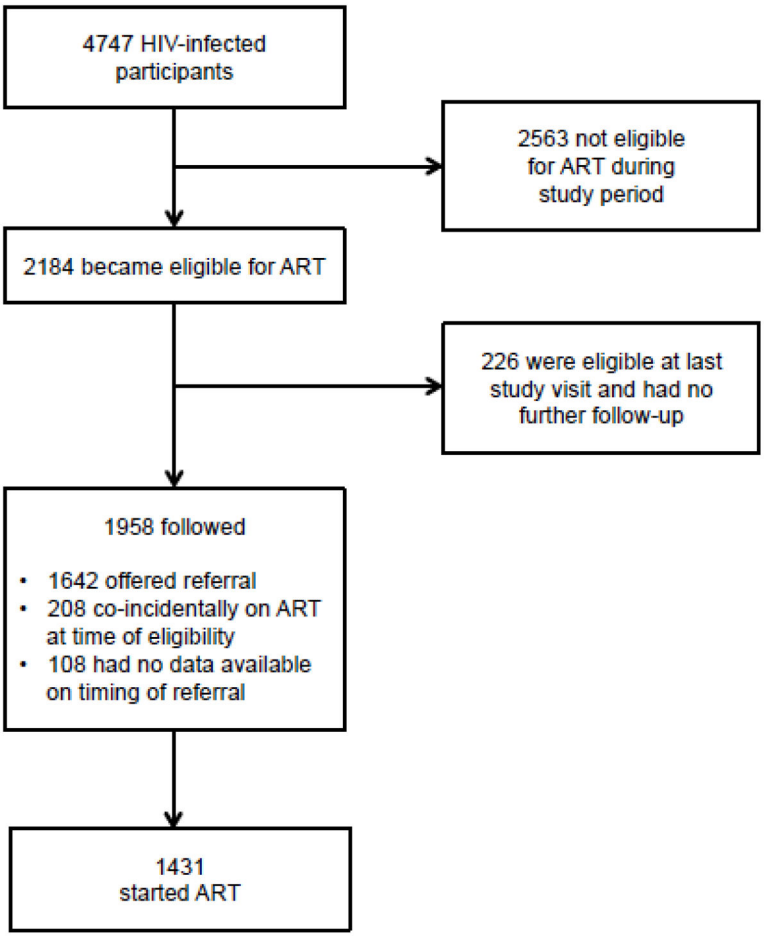

Figure 1.
Follow-up of East African HIV-infected women and men

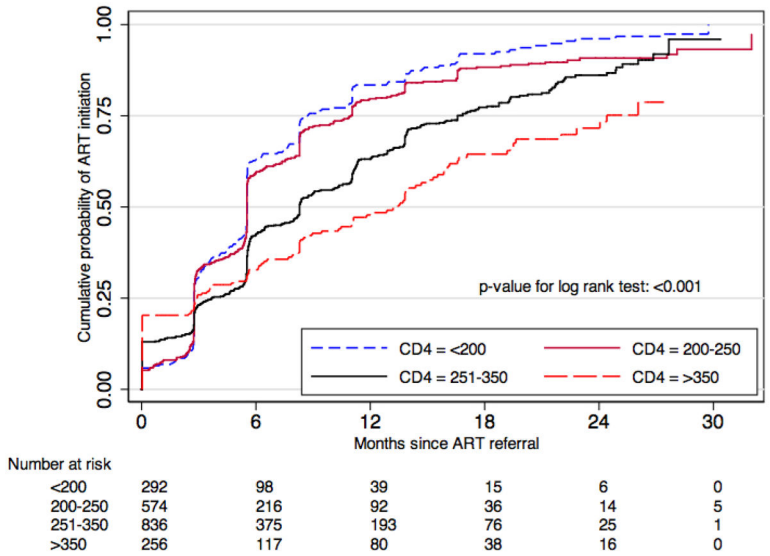

Figure 2.

Cumulative probability of ART initiation, by CD4 count at the time of ART eligibility

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=1958)	
Age in years, median (IQR)	34 (28, 40)	34 (28, 40)	
18–24	828 (17)	259 (13)	
25–34	1922 (41)	776 (40)	
35–44	1443 (30)	659 (33)	
≥45	554 (12)	264 (14)	
Sex			
Women	2962 (62)	1130 (58)	
Men	1785 (38)	828 (42)	
		At enrollment N (%)	**At time of ART eligibility** N (%)
Median CD4 count in cells/μL, (IQR)	496 (375, 662)	391 (320, 495)	273 (221, 330)
<200	0 (0)	0 (0)	292 (15)
200–250	3 (<1%)	2 (<1%)	574 (29)
251–350	919 (19)	690 (35)	836 (43)
>350	3825 (81)	1266 (65)	256 (13)
WHO clinical stage			
1	3006 (63)	1087 (56)	763 (39)
2	1431 (30)	624 (32)	754 (39)
3	310 (7)	247 (13)	402 (20)
4	0 (0)	0 (0)	39 (2)
Trimethoprim-sulfamethoxazole prophylaxis			
Yes	3528 (74)	1455 (74)	1884 (96)
No	1219 (26)	503 (26)	74 (4)
Enrolled in HIV care program separate from the research clinic			
Yes	3256 (69)	1361 (70)	1691 (86)
No	1491 (31)	597 (30)	267 (14)

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)*				
≥35	Referent		Referent	
25–34	1.16 (1.04, 1.29)	0.007	1.05 (0.94, 1.18)	0.38
<25	1.58 (1.34, 1.86)	<0.001	1.39 (1.15, 1.67)	0.001
Sex				
Women	Referent		Referent	Referent
Men	1.18 (1.06, 1.31)	0.002	1.02 (0.91, 1.15)	0.73
Education, (years)*				
≤7	Referent		Referent	Referent
>7	1.36 (1.22, 1.50)	<0.001	1.25 (1.12, 1.39)	<0.001
Monthly income*				
Any	Referent		Referent	Referent
None	1.33 (1.19, 1.48)	<0.001	1.15 (1.02, 1.30)	0.02
Alcohol consumption*				
None	Referent		Referent	Referent
Any	0.81 (0.71, 0.93)	0.003	0.98 (0.87, 1.11)	0.80
Children with partner*				
None	Referent			
Any	0.95 (0.85, 1.08)	0.43		
Unprotected sex with study partner**				
None	Referent		Referent	Referent
Any	0.83 (0.71, 0.97)	0.02	0.89 (0.76, 1.04)	0.14
Clinical Characteristics				
CD4 count (cells/μL)**				
<200	Referent		Referent	
200–250	1.14 (0.99, 1.31)	0.07	1.17 (1.02, 1.35)	0.03
251–350	1.61 (1.41, 1.84)	<0.001	1.43 (1.25, 1.65)	<0.001
>350	2.12 (1.72, 2.61)	<0.001	1.95 (1.58, 2.42)	<0.001
WHO clinical stage**				
3 or 4	Referent			

	Univariate models		Adjusted model	
Characteristic	**Hazard ratio (95% CI)**	**p-value**	**Adjusted hazard ratio (95% CI)**	**p-value**
1 or 2	0.78 (0.69, 0.90)	<0.001		

* At Baseline

** At the time of ART eligibility

Table 3

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

	Initiated ART (n=1102) N (%)	Did not initiate ART (n=466) N (%)
Did not report barriers	752 (68)	180 (39)
Provider barriers		
Required pre-treatment counseling sessions	120 (11)	83 (18)
Repeat CD4 count at clinic greater than eligibility threshold	66 (6)	83 (18)
WHO stage not considered and ART not prescribed	5 (<1)	13 (3)
No ART slots	27 (2)	7 (2)
Personal barriers		
Did not go to referral facility	58 (5)	47 (10)
Stigma	14 (1)	13 (3)
Not ready to start ART	14 (1)	15 (3)
Declined referral	9 (1)	6 (1)
Fear of ART side effects	17 (2)	6 (1)
Feels healthy	15 (1)	6 (1)
Other	5 (<1)	7 (1)