CONCISE COMMUNICATION

Antiretroviral therapy refusal among newly diagnosed HIV-infected adults

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Objective: To determine rates and predictors of treatment refusal in newly identified HIV-infected individuals in Soweto, South Africa.

Design: It is designed as a cross-sectional study.

Methods: We analyzed data from adult clients (>18 years) presenting for voluntary counseling and testing (VCT) at the Zazi Testing Center, Perinatal HIV Research Unit to determine rates of antiretroviral therapy (ART) refusal among treatment-eligible, HIV-infected individuals ($CD4^+$ cell count < 200 cells/μl or WHO stage 4). Multiple logistic regression models were used to investigate factors associated with refusal.

Results: From December 2008 to December 2009, 7287 adult clients were HIV tested after counseling. Two thousand, five hundred and sixty-two (35%) were HIV-infected, of whom 743 (29%) were eligible for immediate ART. One hundred and forty-eight (20%) refused referral to initiate ART, most of whom (92%) continued to refuse after 2 months of counseling. The leading reason for ART refusal was given as 'feeling healthy' (37%), despite clients having a median $CD4^+$ cell count of 110 cells/μl and triple the rate of active tuberculosis as seen in nonrefusers. In adjusted models, single clients [adjusted odds ratio (AOR) 1.80, 95% confidence interval (CI) 1.06–3.06] and those with active tuberculosis (AOR 3.50, 95% CI 1.55–6.61) were more likely to refuse ART.

Conclusion: Nearly one in five treatment-eligible HIV-infected individuals in Soweto refused to initiate ART after VCT, putting them at higher risk for early mortality. 'Feeling healthy' was given as the most common reason to refuse ART, despite a suppressed $CD4^+$ count and comorbidities such as tuberculosis. These findings highlight the urgent need for research to inform interventions targeting ART refusers.

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Introduction

In sub-Saharan Africa, home to 68% of all people living with HIV, [1] mortality rates during the first year of antiretroviral therapy (ART) range from 8 to 26%, with most deaths occurring in the first few months after initiation of ART [2]. An analysis of patients who started ART in four scale-up programs in sub-Saharan Africa from 2004 to 2007 showed early mortality was associated with severity of immunodeficiency and disease status at the initiation of treatment [3]. New WHO guidelines responded to this by recommending earlier HIV diagnosis and ART initiation at a $CD4^+$ cell count of less than 350 cells/μl to reduce early death [4].

South Africa, the country with the most HIV-infected citizens globally, [5] has significantly expanded ART availability since April 2004 for individuals with a $CD4^+$cell count less than 200 cells/μl or WHO stage 4 [6] and currently has the largest ART program in the world [7]. Despite widespread availability of ART, and a National Strategic Plan to expand treatment to at least 80% of HIV-infected treatment-eligible individuals, [8] a substantial unmet need for treatment remains, and roughly only half of ART-eligible patients are actually in care [9].

Prior studies have focused on linkages to care, particularly the impact of loss to follow-up and points of delay in ART initiation on pretreatment mortality [10–12]. Although these factors need to be addressed, there is growing interest in understanding the determinants of ART initiation in sub-Saharan Africa. Little is known about whether delayed ART initiation is due to failure to present for treatment or actual treatment refusal. Our objective was to determine rates and predictors of refusal in newly identified HIV-infected individuals in Soweto, South Africa. Using data collected over the course of 2009 from a high-volume testing center in Soweto, we conducted an analysis to determine the impact of ART refusal on initiation of care, and reasons for refusal in this population.

Methods

Study setting

The Perinatal HIV Research Unit (PHRU) provides free HIV testing, treatment, prevention, and psychosocial support for HIV-infected individuals in Soweto, an urban area in South Africa with one of the highest rates of HIV transmission worldwide. The PHRU has provided on-site voluntary counseling and testing (VCT), funded by the United States Agency for International Development (USAID) and the President's Emergency Plan for AIDS Relief (PEPFAR), since 2001. Zazi Testing Center currently provides rapid HIV tests to over 300 adults (>18 years) monthly, along with family planning and screening for tuberculosis (TB) and sexually transmitted infections (STIs). Clients sign a consent form and are counseled by lay counselors who have undergone intensive training. They are given their HIV results, and, if positive, return for their $CD4^+$ cell counts a week later and referred for treatment as appropriate. Upon referral, clients meet with social workers to discuss ART initiation. Demographics, HIV test results, including $CD4^+$ cell count, STI, and TB results are recorded in a clinical registry. Contact information is for follow-up, referral, and counseling services.

Study participants, eligibility, enrollment, and follow-up procedures

Patients eligible for this analysis included adults (>18 years) who presented to Zazi outpatient center for HIV testing between December 2008 and December 2009 and were found to be HIV-infected and treatment-eligible ($CD4^+$ cell count < 200 cells/μl or WHO stage 4). All treatment-eligible patients were offered free ART onsite. We captured data on patients' willingness to accept treatment upon learning their $CD4^+$ cell count. Those who refused were then counseled by social workers on staff regarding their $CD4^+$ cell count and the clinical criteria associated with an AIDS diagnosis, and followed out for 2 months to assess whether they would be willing to start treatment. Those clients who were diagnosed with active TB were counseled to initiate TB treatment before ART, according to WHO criteria.

This study and data collection instruments were approved by the University of Witwatersrand Ethics Committee (Johannesburg, South Africa) and the Partners Human Research Committee (Protocol #2010-P-001387/1, Boston, Massachusetts). Confidentiality was maintained by use of numbers instead of names during study proceedings and no identifying particulars were documented on interview forms.

Data elements

Patient level data were collected in the following three domains: demographic characteristics – age, sex, marital status, number of children, educational attainment, and employment status; beliefs and behaviors – condom use, alcohol, tobacco, and drug use, willingness to disclose one's HIV status, and history of HIV testing; and laboratory information – dates and results of HIV test, $CD4^+$ cell count, and TB testing. A primary healthcare nurse performed a chart review for each participant to ascertain additional baseline data from the initial clinical evaluation, including a more extensive history for patients refusing treatment. Clients who refused ART were asked to give a single reason for refusal, which was noted by the social worker.

Statistical analysis

We compared two groups in our analysis – specifically HIV-infected, treatment-eligible individuals who accepted ART vs. HIV-infected, treatment-eligible

individuals who refused ART. The rate of ART refusal was calculated as the number of newly diagnosed HIV-infected ART-eligible study participants who actively refused to initiate ART, either upon learning their $CD4^+$ cell count or over a 2-month follow-up period divided by the total number of newly diagnosed HIV-infected ART-eligible study participants.

Quantitative data were double entered into Microsoft Office Excel, and analyses were carried out in STATA (STATA Corp. version 10; College Station, Texas, USA). Baseline factors were compared using χ^2-tests or Fisher's exact test for categorical variables, whereas *t*-tests or Mann–Whitney *U*-tests were used to compare continuous variables across refusal groups. We fitted multiple logistic regression models by considering univariate factors with *P* values of 0.2 or less to investigate factors associated with ART refusal. Changes in log-likelihoods were used to assess factors that significantly explained the odds of ART refusal. The Hosmer–Lemeshow goodness-of-fit test was used to asses the fit of the logistic model to our data.

Results

From December 2008 to December 2009, 7287 adult clients presented for VCT. Of these, 2562 (35%) adults were found to be HIV-infected. Within the HIV-infected cohort, 743 (29%) were eligible to start immediate ART [1]. One-hundred forty-eight HIV-infected ART-eligible clients (20%) refused to initiate treatment upon learning their $CD4^+$ cell counts, and another four clients were either hospitalized or died within a week of their HIV diagnosis. There were few differences between those who agreed to start ART and those who refused (Table 1). The median age of both groups was 34 years and the median $CD4^+$ cell count was 109 cells/μl. Sixty-three percent reported using condoms at their last sexual encounter. Ninety-two percent of ART refusers continued to refuse after 2 months of counseling. Of the 12 clients who ultimately accepted ART after initially refusing, their median CD4 cell count was 113 cells/μl (interquartile range 91–151); their mean age was 35 years (SD 6.8 years); none had active TB; 10 (83%) had an HIV test before; and almost all of them (92%) intended to disclose their HIV status. Reasons given for ART refusal were abstracted from social worker notes and are displayed in Fig. 1. Although six primary reasons were given by respondents, cultural beliefs encompassed both religious (Christian) and ancestral rituals (described as 'super powers that will provide healing') [2].

Single clients were 1.80 times [95% confidence interval (CI) 1.06–3.06] more likely to refuse ART as compared with any other marital status group in adjusted models. Patients with active TB [adjusted odds ratio (AOR) 3.20, 95% CI 1.55–6.61] had higher odds of refusing ART compared with clients who had no evidence of active TB.

Discussion

Despite the dramatic increase in VCT in South Africa in the past few years, with more than half of all South African adults having been tested at least once [13], expansion of testing has not translated into earlier treatment initiation [14]. This is supported by our finding that 70% of VCT clients presenting to the Zazi Testing Center had been previously tested for HIV, yet nearly one in five ART-eligible adults refused treatment within 2 months of diagnosis, leaving them at risk for early mortality. These findings are consistent with rates of pre-ART attrition found at other sites in sub-Saharan Africa [15,16]. Despite VCT being traditionally viewed as an entry point to treatment and care, [17] these data underscore the importance of a new and unappreciated challenge in the cascade of HIV testing to sustained ART.

Although ART-eligible patients not yet in treatment have traditionally been difficult to monitor, we were able to document both rates and reasons for refusal in this VCT population. We found that over 35% of clients who refused ART stated they were 'too healthy' to initiate treatment, despite a median $CD4^+$ cell count of 110 cells/μl. In addition, those with active TB were three times more likely to refuse ART. Prior studies in sub-Saharan Africa have found similar associations between TB positivity and low acceptability of ART [18]. Early ART initiation, particularly in patients with comorbidities such as TB, clearly remains a priority [19]. A recent South African study showing early ART initiation in conjunction with TB therapy in co-infected patients reduced mortality by 56% [20].

Despite 92% of VCT clients initially reporting they would be willing to disclose their status, over 20% of those who refused ultimately stated they were 'unable to disclose.' These results show that the inability to disclose one's status has behavioral consequences and may be more pronounced than initially acknowledged by the general population. Given patients who self-identified as being single were more likely to refuse treatment, the risk for nondisclosure remains concerning among sexually active individuals. This is particularly relevant in light of increasing evidence of the importance of ART treatment in HIV-infected individuals as a form of prevention to uninfected partners [21].

This study has a critical limitation – specifically these data were not collected to examine factors associated with ART refusal. Rather, basic clinical and demographic variables were collected concurrently on patients who accessed VCT. At the time these data were collected, the

Table 1. Characteristics of HIV-infected treatment-eligible individuals.

Variables	HIV-positive with CD4 cell count < 200 cells/μl ($n = 743$)	Agreed to ART ($n = 595$) (80%)	Initial refusers ($n = 148$) (20%)	OR (95% CI)	AOR (95% CI)
Age in years at time of testing, median (IQR)	34	33 (28–39)	34 (28–39)	1.00 (0.98–1.02)	
Sex					
Female	503	401 (67)	102 (69)	1.00	
Male	240	194 (33)	46 (31)	0.93 (0.63–1.37)	
Single/divorced/widow	575	453 (78)	122 (85)	1.62 (0.98–2.69)	1.80 (1.06–3.06)*
Have children	514	414 (86)	100 (87)	1.09 (0.60–2.00)	
Median $CD4^+$ cell count (cells/μl) (IQR)	109	109 (52–164)	110 (58–148)	0.92 (0.67–1.24)	
Level of education					
No education	27	22 (4)	5 (4)	1	
Primary school	51	38 (8)	13 (11)	1.50 (0.47–4.79)	
High school	481	387 (79)	94 (78)	1.07 (0.39–2.90)	
Higher (tertiary)	52	43 (8)	9 (8)	0.92 (0.28–3.08)	
Employed	218	178 (36)	40 (34)	0.92 (0.60–1.41)	
First time testers	232	179 (30)	53 (35)	0.76 (0.52–1.12)	
Intend to disclose	640	511 (92)	129 (93)	1.26 (0.60–2.64)	
Condoms at last sex	398	324 (64)	74 (62)	0.92 (0.61–1.39)	
Use tobacco	155	127 (22)	28 (20)	0.87 (0.55–1.37)	
Use alcohol	264	210 (36)	54 (37)	1.07 (0.73–1.56)	
Use recreational drugs	20	13 (2)	7 (5)	2.23 (0.87–5.70)	
Active TB	34	20 (3)	14 (9)	3.00 (1.48–6.10)**	3.20 (1.55–6.61)**

Data are number and row percentage, unless otherwise noted. AOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; IQR; OR, odds ratio; TB, tuberculosis.
*$P < 0.05$.
**$P < 0.01$.

phenomenon of treatment refusal had not been identified or well understood. Given that, we have no data on clients' understanding of HIV and AIDS and their interpretation of their test results.

As South Africa continues to expand its ART coverage, efforts will need to be made beyond simply testing and counseling to the reach the estimated 2 million people currently in need of treatment. This will require marketing the concept of ART as a life-saving intervention, even for people who report feeling healthy. We have added to the growing literature on understanding factors driving treatment refusal after VCT in South Africa [22,23] by identifying a critical barrier to ramping up accelerated treatment coverage beyond cost reductions, [24] willingness to test, and ART availability. To ensure the success of HIV treatment scale-up in South Africa, it will be essential to understand the reasons for ART refusal in individuals willing to undergo VCT, ultimately enabling the development of effective targeted interventions.

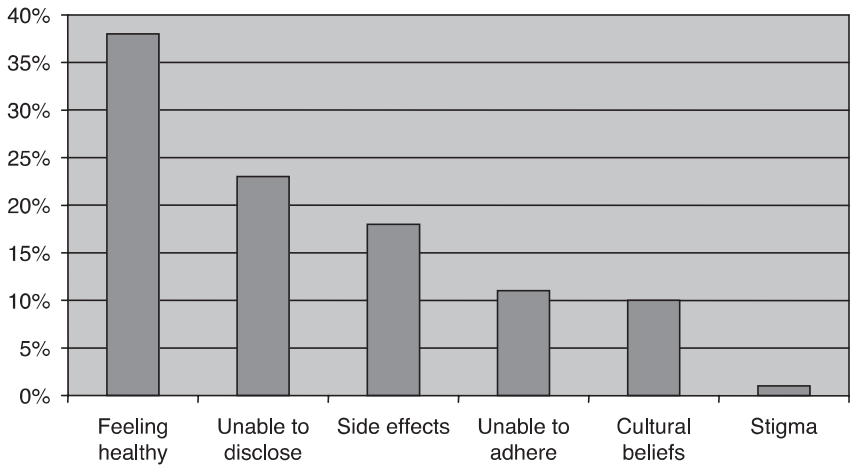

Fig. 1. Percentage of testers who refuse treatment by reason.

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Conflicts of interest

There are no conflicts of interest.

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