Published in final edited form as:
J Acquir Immune Defic Syndr. 2013 March 1; 62(3): 317–321. doi:10.1097/QAI.0b013e3182800daf.

Higher baseline CD4 cell count predicts treatment interruptions and persistent viremia in patients initiating ARVs in rural Uganda

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Abstract

We examined the association between CD4 cell count and adherence in a cohort of Ugandans initiating ARVs. Outcomes were: a) adherence<90%; b) any treatment interruptions>72 hours; c) number of treatment interruptions; and d) HIV RNA>400 copies/ml. We fit regression models to estimate associations with our exposure of interest, baseline CD4 cell count ≥250 cells/μL (n=60) versus <250 cells/μL (n=413). CD4 cell count≥250 cells/μL was independently associated with increased odds and number of treatment interruptions, and increased odds of persistent viremia. Interventions to support adherence in patients with higher CD4 cell counts should be considered as drug availability to this population increases.

Keywords

Adherence; Test and Treat; Uganda; HIV/AIDS; Adherence Monitoring; MEMS

INTRODUCTION

Multiple studies support initiation of HIV antiretroviral (ARV) therapy in healthy individuals at CD4 cell counts above the threshold of risk for opportunistic infections [1-4]. Early initiation of ARV treatment may have substantial public health benefits by reducing the risk of HIV transmission in discordant couples [5]. These findings have provided increased

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This research was presented at the 7th Conference of the International Association of Physicians in AIDS Care in June 2012 in Miami, Florida.

Disclosures:
The authors have no financial disclosures or conflicts of interest.

support for universal testing with immediate ART initiation to prevent both HIV-related morbidity and HIV transmission [6]. Recommending treatment for HIV-infected individuals regardless of CD4 cell count will necessitate offering therapy to increasing numbers of asymptomatic patients, particularly in sub-Saharan Africa, where a large proportion of the HIV-infected population is untreated [7].

While adherence to ARVs in Sub-Saharan Africa has been excellent in general [8], most adherence studies have been limited to people with advanced disease. Advanced disease has significant functional and economic impact on the individual and their family [9]. ARV treatment adherence in resource limited settings is sustained, in part, by tangible support to overcome economic barriers to sustained treatment access [10-12] and is reinforced by functional recovery and subsequent reversal of household economic strains incurred by caring for someone with advanced disease [13,14]. Thus, individuals initiating ARVs at higher CD4 cell counts in these settings might lack elements of social support that sustain early adherence. We examined whether treatment initiation at higher CD4 cell counts is associated with lower adherence and viral suppression in a population of patients initiating ARV therapy in rural Uganda.

METHODS

Study Methods and Patient Population

We performed a prospective observational study of HIV-infected individuals enrolled from a public hospital in southwestern Uganda. Study participants were recruited from the Mbarara Regional Referral Hospital Immune Suppression Syndrome Clinic, which dispenses free ARV therapy in the region. Patients greater than 18 years old who were initiating ARVs and lived within 60 km from the clinic were eligible for study participation. The study was approved by the Mbarara University of Science and Technology and the Partners Human Institutional Review Committees. All participants gave written informed consent.

At the enrollment visit, we collected demographic data including age, marital status, educational attainment, socioeconomic status, self-reported distance from clinic (in minutes of travel-time), self-reported physical functioning (Medical Outcomes Study Physical Health Summary [MOSPHS] Score [15]), screen for heavy drinking (3-item consumption subset of the Alcohol Use Disorders Identification Test [AUDIT-C]) [16], and depression symptom severity (15-item Hopkins Symptom Checklist for Depression, modified for the local context with the addition of a 16th item, “feeling like I don't care about my health”) [17]. Blood was collected for HIV RNA and CD4 cell count at baseline and again at three months. We included participants who had a repeat viral load test within 120 days in the analysis of virologic outcomes. Participants who did not return for a second visit by 120 days were considered loss to follow up.CD4 cell count, our primary exposure of interest, was dichotomized at the threshold of 250 cells/μL.

Adherence measures

ARV adherence was measured using MEMSCap pill bottles (Aardex, Switzerland) which electronically record the date and time of pill bottle opening. Participants were visited at home once monthly and MEMs data was downloaded. Because physical function changes quickly with the initiation of ARV therapy [18], we focused on adherence in the first 90 days as the most sensitive interval to estimate the impact of initial stage of disease on adherence. Our primary outcomes were: a) average adherence in the first 90 days of therapy of less than 90%, b) any treatment interruptions (defined as zero adherence for > 72 hours continuously) in the first 90 days of therapy; c) number of treatment interruptions in the first 90 days of

therapy; and d) persistent detectable HIV viremia at 90 days. We selected a duration of 72 hours based on prior data supporting it as a threshold required to detect viral replication [19].

Statistical Analyses

We compared baseline characteristics between the two exposure groups (CD4 cell count <250 and CD4 cell count≥250 cells/μL) using chi-squared testing for categorical variables and non-parametric ranksum testing for continuous, non-normally distributed variables. For binomial outcomes (adherence <90%, any treatment interruption, persistent viremia), we fit logistic regression models to estimate their associations with our primary explanatory variable of interest, baseline CD4 cell count ≥250 versus <250 cell/μL. For number of treatment interruptions, we fit a negative binomial regression model to estimate the incidence rate ratio comparing those with CD4 cell counts ≥250 versus <250 cell/μL. We employed univariable and multivariable regression modeling to identify potential predictors of adherence including age, sex, marital status, educational attainment (greater than primary education vs. primary education or none), employment, socioeconomic status as measured by the Filmer-Pritchett Asset Index [20], self-reported distance to clinic (>60 minutes of travel time vs. 60 minutes or less), depression symptom severity, positive screen for heavy drinking, and ARV dosing frequency (daily versus more than daily). Because adherence monitoring was censored at the time of death or loss to follow-up, we also repeated analyses allocating those with missing data to poor outcome groups (average adherence <90%, occurrence of at least one treatment gap, and detectable viremia) to assess for potential bias from missing data.

RESULTS

We included 473 participants in the analysis. The majority of participants were female (70.6%) and had a median age of 34 years (interquartile range [IQR], 29-39 years). The median CD4 cell count was 132 cells/μL (IQR 16-200 cells/μl) and the median HIV viral load (log10) was 5.0 copies/ml (IQR 1.6-7.0 copies /ml), (Table 1). The MOS PHS summary score was higher in those with CD4 cell counts ≥250 cells/μL (median 45 vs 40, p=0.01). In the 120 day period after initiation, there were two deaths (3.3%) among participants with a CD4 cell count ≥250 cells/μL and 15 deaths (3.6%) among participants with a CD4 cell count <250 cells/μL. Another 5 (8.6%) and 26 (6.5%) participants in each group respectively were lost to follow-up. Average adherence in the first 90 days was 89.0% across all participants and did not differ by baseline CD4 cell count (p=0.08). Fifty-two participants (10.9%) had at least one treatment interruption of 72 hours and the median duration of interruption was 8 days (IQR 8-18 days). There were approximately twice as many individuals with a CD4 cell count ≥250 cells/μL who had any treatment interruptions compared to those with <250 CD4 cells/μL (20.0% vs 9.7%) (p=0.02). Three hundred fifty-eight participants (75.7%) had a repeat viral load test within 120 days and were included in the analysis of persistent viremia. The proportion of patients with viral suppression on follow-up testing was 19% vs. 9.5%; (p=0.06). There was no difference between groups in the level of viremia upon repeat testing (median 2.2 (log10) copies/ml in both groups, p=0.45)

In multivariable regression models, a CD4 cell count ≥250 was associated with increased odds of any treatment interruption (adjusted odds ratio [AOR] 2.28, 95% confidence interval [CI] 1.01 – 5.15, p=0.048), increased number of treatment interruptions (adjusted incidence rate ratio [AIRR] 2.56, 95%CI 0.99 – 6.65, p=0.054), and increased odds of persistent detectable viremia (AOR 2.83, 95%CI 1.14 – 7.00, p=0.024) (Table 2). CD4 cell count at baseline was not associated with average adherence <90% (AOR 1.40, 95%CI 0.70 – 2.82, p=0.344). In analyses allocating participants who had died or were lost to follow up to poor outcomes, we estimated an attenuated association for odds of treatment interruptions (AOR

1.78, 95%CI 0.88 – 3.60, p=0.108), but a persistent effect for detectable viremia (AOR 2.65, 95%CI 1.08 – 6.52, p=0.034). The association with average adherence <90% was unchanged (AOR 1.60, 95%CI 0.81 – 3.18, p=0.179).

DISCUSSION

We found that individuals starting ARVs at a CD4 cell count ≥250 cells/μL in southwestern Uganda were more likely to experience treatment interruptions in the first three months of therapy and were more likely to have persistent viremia at three months, compared with those starting with a CD4 cell count <250 cells/μL. This finding was despite lower baseline viral load in those initiating therapy with higher CD4 cell counts. While ARV adherence has generally been excellent in resource-limited settings [8,21], these estimates have been based on studies of people with advanced disease, which can have a profound impact on both individuals and their social networks. Social support helps HIV-infected persons overcome severe structural and economic barriers in order to sustain adherence, which in turn restores their health and economic contributions to the social network [11,22]. Relatively healthy, asymptomatic individuals taking ARVs may face the same level of structural and economic barriers, but their treatment course is not characterized by the same changes in functional status as is frequently observed among individuals with advanced disease initiating treatment. Consequently, their initiating of treatment may be less likely to engage the commitment of their social network structural barriers to treatment adherence [22].

Our findings are consistent with variable ARV adherence observed among healthy HIV-infected and HIV-uninfected individuals taking ARVs in the form of pre-exposure prophylaxis (PrEP). As few as 50% of these individuals have detectable drug levels when ARVs are prescribed for preventive purposes [23-25], although adherence to PrEP is higher when HIV-infected sexual partners are included in interventions to increase the provision of support to the HIV-uninfected partner [26,27]. ARV treatment for asymptomatic HIV-infected persons might be analogous in some respects to PrEP, in that it is given to prevent adverse outcomes rather than to restore health. An important distinction between our study and the others described is our use of an observational design (versus an intervention trial), which might be more representative of adherence in similar settings.

While baseline CD4 cell count was associated with treatment interruptions, it was not associated with average adherence. Treatment interruptions particularly predispose individuals to development of resistance to non-nucleoside reverse transcriptase inhibitors [19,21,28], which continue to be first-line therapy in most resource-limited settings.

Our study has several limitations. First, we were not able to characterize the reasons why participants initiated ART. Those with a CD4 cell count ≥250 cells/μL had higher MOS PHS scores, but might not have had improved health status. Some might have been initiated on ARVs for other health events or co-morbidities not captured in the MOS PHS score. While a limitation, unmeasured illness or clinical deterioration in the higher CD4 cell count group would bias the findings to the null. Higher CD4 cell counts, however, might have been associated with other, unmeasured confounders that explain the association we found. A related limitation is that the exposure of interest (high vs low CD4 cell count) was not assigned randomly. In the absence of an experimental study design we are unable to assert that the observed associations are causal. Third, we had relatively few people in the ≥250 cells/μL group (n= 60), which led to wide confidence intervals in our estimated effect sizes.

Further investigation of ARV adherence in relatively healthy individuals in resource-limited settings is recommended to confirm our findings. Moreover, elucidating the factors that cause poor adherence will be vital to developing targeted interventions to improve

outcomes. Though a variety of interventions, including pre- and intra-therapy adherence counseling [29,30], and automated medication reminders,[31] have proven effective, these studies did not target those with relatively high CD4 counts. The efficacy of these and other Interventions specifically targeted to relatively healthy individuals should be pursued as ART is made available to those at higher CD4 count thresholds. Although ARVs have great potential to improve health among those infected, and to prevent transmission to those uninfected [1-3,5,23], healthy individuals receiving ARVs might warrant additional adherence support.

Acknowledgments

We thank the UARTO participants who made this study possible; and Annet Kembabazi and Annet Kawuma, or providing study coordination and support.

Support:

The Uganda AIDS Research and Treatment Outcomes Study is funded by U.S. National Institutes of Health R01 MH54907 and P30 AI27763. The authors also acknowledge the following additional sources of salary support: NIH K23 MH087228 (Haberer); NIH K23 MH096620 (Tsai); NIH K24 MH87227 (Bangsberg); the Harvard Institute for Global Health, the Fogarty International Clinical Research Scholars and Fellows Program at Vanderbilt University (R24 TW007988), and NIH T32 AI007433 (Siedner). Additional study funding was provided by the Mark and Lisa Schwartz Family Foundation, the Sullivan Family Foundation, and the Bacca Foundation.

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Table 1

Summary characteristics for study cohort and by CD4 cell count at enrollment

	Total Cohort (n=473)	CD4<250 cells/μL (n=413)	CD4≥250 cells/μL (n=60)	p-value‡
Baseline Characteristics				
Age (median, IQR)	34 (29-39)	34 (29-39)	36 (29-41)	0.72
Female (%)	70.6	70.5	71.7	0.85
Married (%)	42.7	42.2	48.3	0.38
Achieved Secondary Education or Greater (%)	25.0	26.3	18.6	0.21
Unemployed (%)	26.0	26.0	26.7	0.91
Asset Index (Median, IQR)	-0.5 (-1.6 to 0.9)	-0.3 (-1.5 to 1.0)	-0.8 (-1.8 to 0.6)	0.21
Distance to Clinic in minutes (Median, IQR)	40 (30 – 60)	33 (30 – 60)	43 (20 – 60)	0.71
Depression (%) (HSCL >1.75)	35.7	35.9	36.7	0.91
Audit-C Screen Positive (%)	20.7	22.3	16.1	0.29
Physical Health Summary Score (Median, IQR)	40.4 (31.1 – 49.0)	39.6 (30.2 – 48.5)	44.9 (39.1 – 51.6)	0.01
Daily ARV Dosing (%)	47.6	47.5	50.9	0.63
CD4 Cell Count (median, IQR)	132 (76 – 200)	119 (65-168)	327 (275 – 400)	
Log_{10} HIV Viral Load at baseline (mean, range)	5.0 (1.6 – 7.0)	5.1 (1.6 – 7.0)	4.6 (1.6 – 6.7)	<0.01
Follow-Up Data				
Average Adherence (%)	89.0	89.4	85.7	0.08
HIV Viral Load >400 copies/ml at follow-up visit	10.6	9.5	19.0	0.06
Deaths (n, %)	17 (3.6%)	15 (3.6%)	2 (3.3%)	0.91
Lost to follow up (n, %)	31 (6.8%)	26 (6.5%)	5 (8.6%)	0.56

‡Tests of association between the two exposure groups (CD4 cell count <250 and CD4 cell count ≥250 cells/μL) were performed using chi-squared testing for categorical variables and non-parametric ranksum testing for continuous, non-normally distributed variables

Table 2

Univariable and multivariable regression analysis for associations between a baseline CD4 cell count ≥250 cells/μL and various ARV adherence measures in the first 3 months of therapy among a population of patients initiating anti-retroviral therapy in southwest Uganda (n=473).

	Univariable Model			Multivariable Model †		
	Estimate¥	95% CI	p-value	Estimate¥	95% CI	p-value
Outcome 1: Any treatment interruptions > 72 hours						
Baseline CD4 cell count ≥250 cells/μL	2.33	1.14 – 4.75	0.020	2.28	1.01 – 5.15	0.048
Outcome 2: Number of treatment interruptions > 72 hours						
Baseline CD4 cell count ≥250 cells/μL	2.26	0.91 – 5.64	0.079	2.56	0.99 – 6.65	0.054
Outcome 3: Average Adherence > 90%						
Baseline CD4 cell count ≥250 cells/μL	1.44	0.78 – 2.64	0.243	1.40	0.70 – 2.82	0.344
Outcome 4: Detectable HIV Viremia						
Baseline CD4 cell count ≥250 cells/μL	2.24	0.95 – 5.29	0.065	2.83	1.14 – 7.00	0.024

†Multivariable models were adjusted for the following: age, gender, marital status, educational attainment, employment status, Filmer-Pritchett asset index, self-reported distance to clinic, Hopkins Symptoms Checklist for Depression, positive screen for heavy drinking, ARV dosing frequency.

¥Estimates of association for any treatment interruptions, average adherence, and detectable viremia represent odds ratios and adjusted odds ratios. Estimates of association for number of treatment interruptions represent incidence rate ratios and adjusted incident rate ratios.