CD4$^+$ cell count at antiretroviral therapy initiation and economic restoration in rural Uganda

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Objective: To determine whether earlier initiation of antiretroviral therapy (ART) is associated with better economic outcomes.

Design: Prospective cohort study of HIV-positive patients on ART in rural Uganda.

Methods: Patients initiating ART at a regional referral clinic in Uganda were enrolled in the Uganda AIDS Rural Treatment Outcomes study starting in 2005. Data on labor force participation and asset ownership were collected on a yearly basis, and CD4$^+$ cell counts were collected at pre-ART baseline. We fitted multivariable regression models to assess whether economic outcomes at baseline and in the 6 years following ART initiation varied by baseline CD4$^+$ cell count.

Results: Five hundred and five individuals, followed up to 6 years, formed the estimation sample. Participants initiating ART at CD4$^+$ cell count at least 200 cells/μl were 13 percentage points more likely to be working at baseline ($P < 0.01$, 95% confidence interval 0.06–0.21) than those initiating below this threshold. Those in the latter group achieved similar labor force participation rates within 1 year of initiating ART ($P < 0.01$ on the time indicators). Both groups had similar asset scores at baseline and demonstrated similar increases in asset scores over the 6 years of follow-up.

Conclusion: ART helps participants initiating therapy at CD4$^+$ cell count below 200 cells/μl rejoin the labor force, though the findings for participants initiating with higher CD4$^+$ cell counts suggests that pretreatment declines in labor supply may be prevented altogether with earlier therapy. Baseline similarities in asset scores for those with early and advanced disease suggest that mechanisms other than morbidity may help drive the relationship between HIV infection and economic outcomes.

AIDS 2014, **28**:1221–1226

Keywords: antiretroviral therapy, CD4$^+$ cell count, economic restoration, employment, HIV, sub-Saharan Africa, Uganda, wealth

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Received: 28 October 2013; revised: 18 December 2013; accepted: 18 December 2013.

DOI:10.1097/QAD.0000000000000188

Introduction

The WHO recently recommended earlier initiation of antiretroviral therapy (ART), in particular at $CD4^+$ T-cell lymphocyte cell ($CD4^+$) count above 500 cells/μl [1]. These guidelines are based on evidence that earlier initiation reduces morbidity and mortality and lowers the risk of HIV transmission [2–4]. Earlier initiation may confer significant economic benefits as well. A growing body of work has shown that ART helps individuals resume employment after having been too sick to work [5–14]: earlier ART may prevent the pretreatment declines in socioeconomic status altogether [15]. Moreover, earlier therapy may also augment subsequent economic recovery if those initiating ART at lower $CD4^+$ cell counts have difficulty achieving their pretreatment economic status, perhaps due to reduced productivity from persistent morbidity or lower social mobility.

At present, the relationship between $CD4^+$ cell count at initiation and the trajectory of economic status is not well understood. A recent study demonstrated that individuals with $CD4^+$ cell count above 200 cells/μl in a rural Ugandan parish had similar labor force participation rates as HIV-negative individuals [15]. However, this study did not explicitly focus on individuals on ART, nor did it examine differences in economic outcomes over time. To address this gap, we used data from an HIV cohort in rural Uganda to examine whether earlier initiation of ART was associated with a higher labor force participation rates and greater household asset ownership, both at ART initiation and through 6 years of follow-up.

Methods

Participants, setting, and data

We used data from the Uganda AIDS Rural Treatment Outcomes (UARTO) Study, an ongoing cohort study of HIV-infected individuals initiating ART in rural, southwestern Uganda, started in 2005. Previously, ART-naive persons 18 years of age or older initiating ART at the Immune Suppression Syndrome Clinic of the Mbarara Regional Referral Hospital were eligible for enrollment. Survey instruments were translated into the local Bantu language Runyankole, with interviews conducted by a native Runyankole speaker. Ethical approval for the study was obtained from the Mbarara University of Science and Technology Institutional Review Committee, the Committee on Human Research at the University of California at San Francisco, and the Partners Healthcare Human Research Committee. Consistent with national guidelines, clearance for the study was granted by the Uganda National Council for Science and Technology and the Research Secretariat in the Office of the President.

Participants provided information on socioeconomic status and basic demographic characteristics at baseline and at yearly intervals thereafter. Our primary outcomes of interest were labor force participation and household asset ownership. Participants who reported engagement in any income-generating activity, whether in the informal (self-employment in trades, agriculture, etc.) or formal sectors at the time of survey were considered as participating in the labor force. For asset ownership, we created an index representing the number of reported assets owned by the household out of 16 different durable goods (see Table 1 notes). Our primary explanatory variable of interest was baseline $CD4^+$ cell count, which was obtained via serum samples for all participants prior to initiating ART. We partitioned the sample into persons initiating ART at $CD4^+$ cell count below 200 cells/μl vs. those initiating ART at $CD4^+$ at least 200.

Statistical analysis

We first plotted unadjusted trends in labor force participation by $CD4^+$ cell count at initiation. Second, we fitted a probit regression model specifying labor force participation as the outcome variable and the following explanatory variables: the baseline $CD4^+$ cell count (<200 vs. ≥ 200 cells/μl); a set of binary indicators for each year since ART initiation; and interactions between the $CD4^+$ cell count and year indicators, so as to test whether the labor supply response to ART differed between the $CD4^+$ groups. We adjusted our models for age and age-squared interacted with sex, educational attainment, marital status, and season of interview (March–May and October–November rainy seasons). We presented labor force participation estimates as marginal effects (i.e. the percentage point increase in the probability of observing the dependent variable corresponding to a one-unit change in a continuous explanatory variable or a change from 0 to 1 for a dichotomous explanatory variable). For the household asset scores, we fitted regression models using ordinary least squares.

For both labor force participation and asset scores, we examined trends through 6 years after ART initiation. All analyses were conducted using Stata/SE 13.0 (Stata Corp, College Station, Texas, USA).

Results

Our sample consisted of 505 participants: 325 initiated ART at $CD4^+$ cell count below 200 cells/μl and 180 initiated ART at $CD4^+$ at least 200. Within the latter group, the median $CD4^+$ cell count at initiation was 284 cells/μl [interquartile range (IQR) 233–360], with 47 (26%) initiating ART at $CD4^+$ at least 350 cells/μl. Women comprised 70% of the sample and participants were, on average, surveyed at five annual time points. At

baseline, participants initiating ART at $CD4^+$ cell count at least 200 cells/μl were more likely to be working compared to those initiating ART at $CD4^+$ below 200 (70 vs. 56%; $\chi^2 = 9.15$, $P < 0.01$), but had similar asset index scores. Apart from marriage, there were no statistically significant differences in baseline characteristics (Table S1, http://links.lww.com/QAD/A465).

Figure 1 represents unadjusted trends in labor force participation and asset ownership. Although participants initiating ART at $CD4^+$ cell count below 200 cells/μl were less likely to be working at baseline, within 1 year of treatment initiation, their average labor force participation rate converged to that of the participants initiating ART at $CD4^+$ at least 200 cells/μl. There were moderate increases for both groups thereafter, with participation rates around 80% at 6-year follow-up (Fig. 1a). For asset scores, both groups started at similar levels and experienced gradual increases after initiating ART (Fig. 1b).

The multivariable regression results, shown in Table 1, were consistent with the patterns in Fig. 1. As indicated by the regression coefficients on the $CD4^+$ cell count variable, participants initiating ART at $CD4^+$ at least 200 cells/μl were 13 percentage points more likely to be working at baseline [column 1; $b = 0.13$, 95% confidence interval (CI) 0.06–0.21]. This group experienced little change in labor force participation rates over baseline in the ensuing years: the sum of the interacted and noninteracted yearly indicator variables (which recovers the total change in participation rates relative to baseline for participants initiating ART at $CD4^+$ cell count at least 200 cells/μl) was effectively zero for most of the 6 follow-up years. Those initiating at $CD4^+$ below 200 cells/μl, however, did experience increased labor force participation: the coefficients on the uninteracted yearly indicator variables indicate a 12–20 percentage point increase in the probability of working over baseline for each follow-up year ($F = 61.24$, $P < 0.01$).

For asset scores (column 2), participants in the high $CD4^+$ cell count group owned a similar number of assets at baseline, and experienced gradual similar increases after starting ART, as participants in the low $CD4^+$ cell count group: the time dummies were collectively statistically significant ($F = 6.25$, $P < 0.01$), but the coefficients on the interactions with the $CD4^+$ cell count dummy were not. For both models, the associations between the outcomes and schooling, sex, and age were in the expected directions (Table S2, http://links.lww.com/QAD/A465).

We additionally estimated models including individual fixed effects, to control for time-invariant individual level confounders; the results were unchanged. In addition, we also excluded from the analysis all women who reported being pregnant at baseline (since they may have been less likely to work and more likely to access ART at higher $CD4^+$ cell counts). The substantive results again were unchanged. We also considered sample attrition and missing interview data, and ruled this out as a major source of bias in our comparisons of economic outcomes between the high and low $CD4^+$ groups (see Table S3, http://links.lww.com/QAD/A465 and associated notes). Finally, we examined whether economic status at baseline and over time differed for those initiating at $CD4^+$ cell count at least 350 cells/μl. As shown in Figure S1 and Table S4 (http://links.lww.com/QAD/A465), outcomes at baseline and at 1–2 years of follow-up were substantively similar to those for initiating at $CD4^+$ cell count above 200 and below 350 cells/μl, although small sample sizes (only 47 participants initiated therapy at $CD4^+$ at least 350 cells/μl) precluded any definitive interpretation.

Discussion

Results from this cohort study of HIV-infected adults on ART in rural Uganda showed that participants initiating ART at $CD4^+$ cell count at least 200 cells/μl started out with higher labor force participation rates relative to their counterparts, initiating ART at $CD4^+$ below 200. Within 1 year after starting ART, however, those initiating ART at $CD4^+$ below 200 cells/μl had caught up and thereafter maintained similar trajectories in labor force participation: the overall 6-year change in likelihood of working for adults initiating at $CD4^+$ cell count below 200 cells/μl was 20 percentage points. Interestingly, despite being more likely to be working at baseline, participants with higher $CD4^+$ cell counts at initiation reported similar household asset scores as the lower $CD4^+$ cell count group, with both groups experiencing increases in asset ownership over the study period.

These results have several policy implications. Whereas those initiating ART at $CD4^+$ cell count below 200 cells/μl caught up quickly and experienced similar trajectories thereafter, earlier ART initiation may have prevented households from experiencing job loss and economic hardship in the first place, consistent with recent findings by Thirumurthy *et al.* [15]. Focusing on labor force participation alone, however, may mask more subtle impacts of HIV on individual and household socioeconomic outcomes. In particular, despite being more likely to work, participants with higher baseline $CD4^+$ cell counts started with similar asset scores as those initiating ART at lower $CD4^+$ cell counts. It may be that durable assets were being sold to make up for unmeasured declines in productivity or that participants, prior to treatment initiation, perceived shorter life expectancies and therefore did not undertake long-term investments in productive assets [16]. These alternate mechanisms deserve further attention and motivate economic interventions at the time of diagnosis in order to prevent

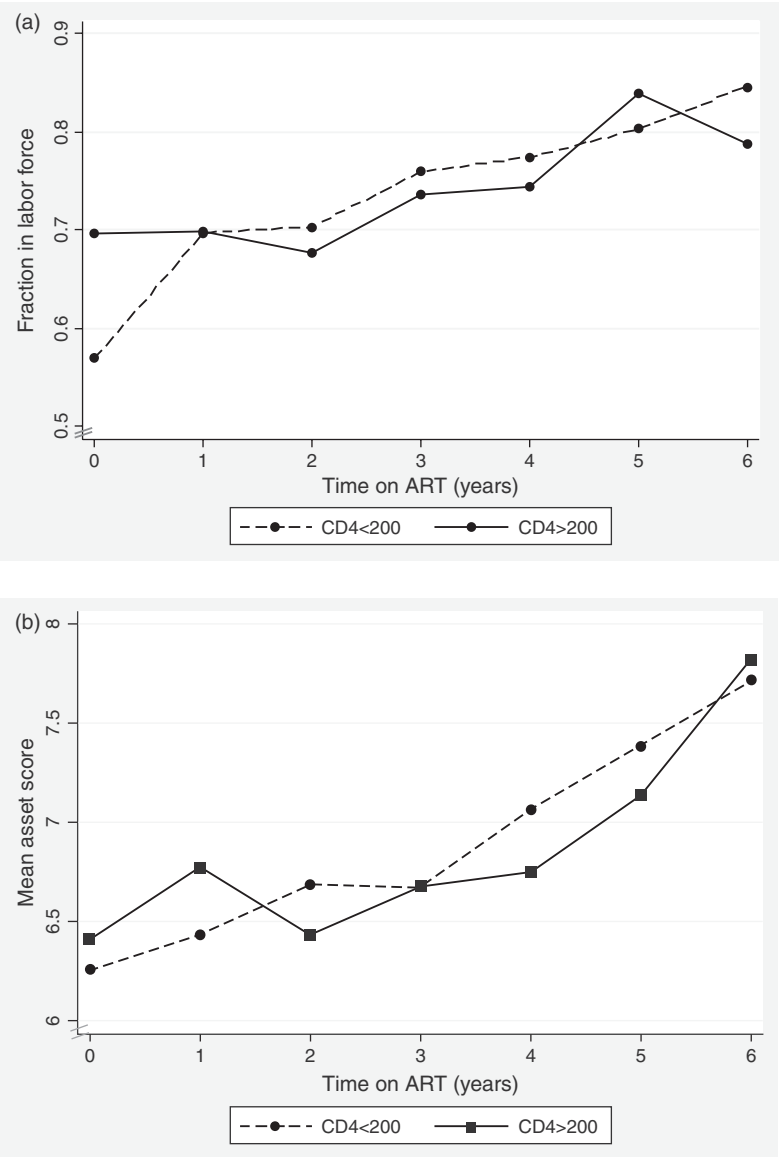

Fig. 1. Trends in labor force participation and household asset scores by CD4$^+$ cell count at time of ART initiation. The figures display means of the outcome variables at each time point. Labor force participation = 1, if the participant reported being engaged in any formal or informal income-generating activity; hence the mean is the proportion of the sample working at that time point. Asset score ranges from 0 to 16 (see Table 1 notes for details on construction). Time on ART = 0 refers to pre-ART baseline. CD4 refers to CD4$^+$ cell count at the time of ART initiation. Confidence intervals were not displayed so as to improve readability: only the differences in baseline labor force participation in panel a were statistically significant ($P < 0.01$).

nonmorbidity-related economic decline. Finally, continued improvements in socioeconomic position for all study participants 6 years after ART initiation demonstrates that economic impacts of ART may persist well after immune reconstitution is achieved.

The study has several limitations. First, the nonexperimental study design limited our ability to make causal inferences. Second, we did not observe economic status prior to the baseline survey, limiting our ability to characterize the trajectory of pre-ART economic status. Third, we lacked data on alternate economic measures such as hours worked or wage earnings, which would have enabled us to better characterize subtle differences in productivity across the different CD4$^+$ cell count groups over the course of ART. Finally, it is unclear whether our findings generalize to other settings, though similarities in ART-led economic recovery across different countries suggest that some degree of generalization is reasonable [6,10,11].

Understanding the relationship between timing of ART initiation and economic deterioration is important for the design of ART guidelines and the valuation of the

Table 1. Association between CD4$^+$ cell count at baseline and trends in labor force participation and household asset ownership.

	1	2
	Labor force participation	Asset score
Baseline CD4$^+$ cell count (cells/μl)		
<200	Ref	Ref
≥200	0.13 (0.057, 0.21)***	0.0049 (−0.47, 0.48)
Time on ART (years)		
Baseline	Ref	Ref
1	0.12 (0.051, 0.18)***	0.16 (−0.23, 0.56)
2	0.12 (0.057, 0.19)***	0.39 (−0.016, 0.80)*
3	0.16 (0.10, 0.22)***	0.27 (−0.12, 0.66)
4	0.18 (0.12, 0.24)***	0.70 (0.30,1.10)***
5	0.19 (0.13, 0.25)***	0.95 (0.52,1.38)***
6	0.20 (0.13, 0.28)***	1.17 (0.65, 1.70)***
Time on ART × CD4$^+$ group interactions		
1 year × CD4$^+$ ≥200	−0.12 (−0.24, 0.013)*	0.21 (−0.48, 0.90)
2 years × CD4$^+$ ≥200	−0.16 (−0.31, −0.001)**	−0.47 (−1.24, 0.30)
3 years × CD4$^+$ ≥200	−0.18 (−0.33, −0.025)**	−0.2 (−0.93, 0.52)
4 years × CD4$^+$ ≥200	−0.13 (−0.29, 0.026)	−0.31 (−1.11, 0.49)
5 years × CD4$^+$ ≥200	−0.07 (−0.26, 0.12)	−0.11 (−0.93, 0.71)
6 years × CD4+ ≥200	−0.20 (−0.44, 0.038)*	0.33 (−0.81, 1.47)
Number of participants	505	505
Person-years	2349	2349

Regression coefficients are reported with 95% confidence intervals in parentheses. Each column represents a separate regression. Models for labor force participation were estimated using probit regression, with the dependent variable equal to 1 if the individual reported participation in any formal or informal income-generating activity at the time of interview. All models included controls for baseline age, age-squared, a binary variable for sex, interactions between sex and baseline age, and binary indicators for marital status, completing some secondary schooling, and interview during the rainy season (see Table S2, http://links.lww.com/QAD/A465 for coefficient estimates on covariates). Reported coefficients are marginal effects. These can be interpreted as follows: for a continuous variable, the marginal effect coefficient reflects the percentage point increase in the probability of observing the dependent variable for a 1 unit change in the explanatory variable; for binary variables, it reflects a similar change in the dependent variable associated with a change from 0 to 1 on the explanatory variable of interest. Models for asset scores (integer ranging from 0 to 16, representing the count of the number of assets owned from the following: iron, gas or electric stove, refrigerator, telephone, motorbike, bicycle, car, clock, television, radio, bed, sofa, lantern, cupboard, and mattress) were estimated using ordinary least squares regressions. For all models, the main explanatory variables were CD4$^+$ cell count at baseline and their interactions with the time-on-ART dummy variables. The 'Number of participants' refers to the number of unique individuals in the estimation sample. 'Person-years' refers to the total number of person-year observations.
*$P < 0.10$.
**$P < 0.05$.
***$P < 0.01$.
Confidence intervals computed using heteroskedasticity correct standard errors.

economic benefits of early ART initiation. Our study demonstrates that initiating ART at CD4$^+$ cell count above 200 cells/μl may have helped prevent job loss, though perhaps it did not help stave off losses in household assets. Future research should examine a broader set of socioeconomic outcomes across a wider range of baseline CD4$^+$ cell counts (in particular the 350 and 500 cells/μl thresholds identified in the 2010 and 2013 WHO guidelines), most optimally in the setting of a randomized controlled trial, to better identify ART initiation thresholds in which economic status is not compromised.

Acknowledgements

We thank the UARTO participants and staff for making this study possible. We also thank three anonymous referees for their helpful comments.

Author contributions: A.S.V. took the lead on the conception and design of the analysis, performed data analysis, wrote the first draft of the article, and gave final approval of the version to be published.

H.T., J.E.H., Y.B.II, A.K., P.W.H., J.N.M. and D.R.B. assisted with study conception and design, interpretation of the results, made substantial edits and critical revisions to the article, and gave final approval of the version to be published.

M.J.S. assisted with the interpretation of the results, made substantial edits and critical revisions to the article, and gave final approval to the version to be published.

A.C.T. supervised study conception and design of the analysis, assisted with interpretation of the results, made substantial edits and critical revisions to the article, and gave final approval of the version to be published.

Funding sources: The Uganda AIDS Rural Treatment Outcomes (UARTO) study is funded by the US National Institutes of Health (NIH) R01MH054907 and P30A1027763. The authors also acknowledge salary

support through K23MH087228, K24MH087227, K23 MH087228, K01HD061605, and K23MH096620.

Conflicts of interest

The authors have no conflicts of interest to report.

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