

RESEARCH ARTICLE

Socioeconomic position and ten-year survival and virologic outcomes in a Ugandan HIV cohort receiving antiretroviral therapy

Andrew G. Flynn^{1*}, Godwin Anguzu¹, Frank Mubiru¹, Agnes N. Kiragga¹, Moses Kanya², David B. Meya^{1,3}, David R. Boulware³, Andrew Kambugu^{1,3}, Barbara C. Castelnuevo¹

1 Infectious Diseases Institute, Kampala, Uganda, **2** School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda, **3** Department of Medicine, University of Minnesota, Minneapolis, Minnesota, United States of America

* apgflynn@gmail.com



Abstract

Lifelong ART is essential to reducing HIV mortality and ending the epidemic, however the interplay between socioeconomic position and long-term outcomes of HIV-infected persons receiving antiretroviral therapy (ART) in sub-Saharan Africa is unknown. Furthering the understanding of factors related to long-term ART outcomes in this important region will aid the successful scale-up of ART programs. We enrolled 559 HIV-infected Ugandan adults starting ART in 2004–2005 at the Infectious Diseases Institute in Kampala, Uganda and followed them for 10 years. We documented baseline employment status, regular household income, education level, housing description, physical ability, and CD4 count. Viral load was measured every six months. Proportional hazard regression tested for associations between baseline characteristics and 1) mortality, 2) virologic failure, and 3) mortality or virologic failure as a composite outcome. Over ten years 23% (n = 127) of participants died, 6% (n = 31) were lost-to-follow-up and 23% (107/472) experienced virologic treatment failure. In Kaplan-Meier analysis we observed an association between employment and mortality, with the highest cumulative probability of death occurring in unemployed individuals. In univariate analysis unemployment and disease severity were associated with mortality, but in multivariable analysis the only association with mortality was disease severity. We observed an association between higher household income and an increased incidence of both virologic failure and the combined outcome, and an association between self-employment and lower incidence of virologic failure and the combined outcome when compared to unemployment. Formal education level and housing status were unrelated to outcomes. It is feasible to achieve good ten-year survival, retention-in-care, and viral suppression in a socioeconomically diverse population in a resource-limited setting. Unemployment appears to be related to adverse 10-year ART outcomes. A low level of formal education does not appear to be a barrier to successful long-term ART.

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Introduction

Socioeconomic position—an aggregate of resources including education, employment, income and wealth that interact but are not interchangeable—is linked to health outcomes in a variety of diseases and settings.[1–4] Among HIV-infected individuals receiving antiretroviral therapy (ART) in high-income countries, less wealth, income or formal education conveys risk for poorer survival.[5–11] Similarly, food insecurity, less formal education and homelessness conveys risk for decreased viral suppression in high-income countries.[5, 12, 13] However, although HIV/AIDS is the leading cause of death in sub-Saharan Africa and the number of individuals receiving ART is increasing,[14, 15] any relationship between socioeconomic position and ART outcomes in this important region is poorly understood.

Scale-up of ART and viral load monitoring in sub-Saharan Africa is recent and limited[15] and, as a result, most literature on socioeconomic determinants examines pre-ART outcomes. Regional literature indicates higher socioeconomic position may convey an increased risk of HIV infection among the general population and, among HIV-infected individuals in care before starting ART, lower socioeconomic position may convey an increased risk of loss-to-follow-up and death.[16–25] The limited literature examining socioeconomic position and ART outcomes in Africa is plagued by short follow-up times. Studies report a higher relative one-year mortality among ART patients with less wealth, no regular income, no formal education, and unemployment,[26, 27] and in Uganda unemployment has been associated with two-fold higher four-year mortality on ART.[28] These African studies did not account for physical ability and disability, which is related to disease progression and death in people living with HIV, and may also be related to socioeconomic position.[29] Despite the fact that viral monitoring is the most objective measure of ART adherence and subsequent treatment success, regional literature examining socioeconomic position and viral suppression is limited to one 2003 South African study which reported no association between socioeconomic position and one-year viral suppression when ART was provided free of charge.[30]

Despite an incomplete understanding of the interplay between socioeconomic position and ART outcomes, a myriad of interventions have been proposed and implemented by NGOs and even ministries of health in sub-Saharan Africa to address financial and social barriers to successful ART.[31, 32] Furthering the understanding the complicated relationship between socioeconomic position and outcomes of HIV is crucial for these programs to complement ART and viral load scale-up and achieve the best possible outcomes. Our study, conducted at a free ART clinic in Kampala, Uganda, provides Africa's first rigorous long-term assessment of the associations between different social and economic factors and the risk of mortality and virologic failure after ART initiation in a large, socioeconomically diverse, observational HIV cohort with low loss-to-follow-up and regular viral load testing. As successful lifelong ART is the cornerstone of strategies to reduce HIV mortality and end the HIV epidemic, understanding the factors related to long-term ART outcomes is essential.

Methods

This prospective cohort study enrolled HIV-infected ART-naïve Ugandan adults ≥ 18 years of age who initiated ART between April 2004 and April 2005 at the Infectious Disease Institute clinic in Kampala, Uganda. Participants were followed for ten years. Eligibility criteria included at least two previous clinic visits, stable residence within 20 kilometers of Kampala, CD4 count < 200 cells/ μL or WHO stage IV disease, and written informed consent. At enrollment, we assessed HIV progression with baseline CD4 count, and we measured disability with the Karnofsky performance scale, which predicts mortality in HIV-infected persons.[29] A Karnofsky score < 80 indicates difficulty with physical tasks.[33] The first-line ART regimen,

initiated upon enrollment in the cohort, was stavudine or zidovudine plus lamivudine and either nevirapine or efavirenz. The study was approved by the Makerere University Ethics Committee and the Uganda National Council for Science and Technology Ethics Committee and written consent was obtained from each participant. More detailed descriptions of study procedures and data collection have been previously reported.[34, 35]

Measuring socioeconomic position

At cohort enrollment, we interviewed participants to record baseline socioeconomic characteristics. Self-reported monthly household income was converted to USD and categorized as above or below 1 USD/day. We assessed: 1) highest level of schooling completed (primary or below, any secondary, or any post-secondary); 2) household income (no regular income, regular income below the 2004 international poverty line of 1 USD/day, and regular income above 1 USD/day); 3) employment status (unemployed, self-employed, employed by government/organization and employed by a private company) and 4) housing description (brick or mud). Self-employment was defined as the state of working for oneself, such as growing/creating products to sell or owning a small business, without an employer.

Ascertainment of clinical outcomes

Clinic visits were scheduled every 6 months and participants were classified as lost to follow-up if they missed a clinic visit and were unreachable by telephone and home visit. Deaths were recorded and confirmed through medical record review and interviews with participants' next of kin. HIV-1 viral load was measured in all participants at enrollment and afterwards every 6 months (Amplicor HIV-1 Monitor PCR Test version 1.5 with a detection limit of 400 copies/mL through 2011 and, more recently, using COBAS Ampliprep/COBAS Taqman HIV-1 Test Ver.2.0, Roche Diagnostics, Indianapolis, IN). Virologic treatment failure was defined as either lack of initial virologic suppression (at least one measurement below 400 copies/mL after ART initiation) or, after achieving initial suppression, two consecutive measurements >1000 copies/mL or one measurement >5000 copies/mL among patients who had no follow up measurement.[36, 37]

Statistical analysis

We described baseline cohort clinical and socioeconomic characteristics stratified by sex. For categorical variables we compared proportions using the chi-square test and for continuous variables we compared medians using the Kruskal-Wallis test. We used Kaplan-Meier survival methods to calculate survival time and time to treatment failure stratified by baseline socioeconomic characteristics. Patients who died were followed up to known date of death or date of last clinic visit if death date unknown. Patients who were lost-to-follow-up were censored on last visit date, while all patients alive at ten years were administratively censored on the date of their ten-year clinic visit. For treatment failure, follow-up time began at the month six clinic visit or the first date of viral suppression and was calculated until the date of viral failure among those who failed. Among patients who died, who were lost-to-follow-up or who completed ten years of ART without failure, follow-up time was calculated until the date of death, the last visit seen or the ten-year clinic visit, respectively.

To estimate the predictive associations between socioeconomic variables and mortality and virologic treatment failure, we performed Cox proportional hazard regression for each outcome (1) mortality, 2) treatment failure and 3) composite outcome of mortality and treatment failure) including demographic and socioeconomic variables as well as baseline and time-varying CD4 count and functional impairment (Karnofsky score). We developed a multivariable

model that included age, gender and other variables that reached $p \leq 0.25$ in univariate analysis. Robust standard errors were used to account for within-patient correlation. Analysis was performed using Stata version 12 (Stata Corp, College Station, Texas).

Results

We enrolled a total of 559 adults starting ART between April 2004 and April 2005. Demographic, socioeconomic and clinical characteristics at enrollment separated by gender are presented in [Table 1](#). Median age was 35 years (IQR 30–41), 69% ($n = 386$) were women, and women participants were younger than men ($p = 0.001$). At baseline, 49% ($n = 272$) were unemployed, 46% ($n = 257$) had a primary school education or less, 68% ($n = 378$) reported no regular household income or income below the poverty line of USD <1/day, and 33% ($n = 187$) lived in a mud house. Women had lower socioeconomic indicators than men ($p < 0.001$) except in housing, which did not differ ($p = 0.32$). Of 553 participants with CD4 count measured at enrollment, 53% ($n = 292$) had a CD4 count <100 cells/ μL . Participants with CD4 <100 were more likely unemployed (55%) than those with higher CD4 >100 cells/ μL (42%, $p = 0.04$). At baseline, 34% (189/559) were functionally impaired with a Karnofsky performance scale <80. Compared to participants with no functional impairment, a larger proportion of those with a Karnofsky <80 were unemployed (70% vs 38%, $p < 0.01$) and receiving no regular income or any income <1 USD/day (81% vs 61%, $p < 0.01$). After ten years, 6% ($n = 31$) of participants were lost to follow-up. In Kaplan-Meier analysis, sex and employment status were associated with loss to follow-up, with men and unemployed individuals most likely to be lost from the cohort.

Mortality

After ten years, 72% (401/559) of participants were alive and in care at our clinic and 23% ($n = 127$) had died with 63% ($n = 80$) of deaths in the first year of HIV therapy. Kaplan-Meier survival analysis showed higher cumulative probability of death among participants with baseline CD4 <100 cells/ μL ($p < 0.01$), among participants with Karnofsky <80 indicating baseline functional impairment ($p < 0.01$), and among participants who were unemployed at enrollment ($p < 0.01$). In the univariate proportional hazard regression age >40 years compared to a reference age <30 was associated with poorer survival, while Karnofsky score >80 and CD4 100–200 cells/ μL compared with <100 were associated with improved survival (Table A in [S1 File](#)). Self employment or employment by government or an organization compared with unemployment, Karnofsky score >80 and CD4 of 100–200 cells/ μL compared to <100 were all associated with improved survival. In the multivariable proportional hazard regression, compared to a reference age of <30 years, age between 30 and 40 years and >40 years was significantly associated with death. Karnofsky performance score >80 and baseline CD4 count of 100–200 cells/ μL compared to CD4 <100 cells/ μL were significantly associated with lower risk of mortality. No socioeconomic characteristics were significantly related to mortality in the multivariable model.

Virologic treatment failure

Of the initial 559 participants, 84% ($n = 472$) were still alive and had at least one viral load measurement after 6 months of ART. Over the ten year period 23% (107/472) met the definition of virologic treatment failure, including 7% (33/472) who never achieved viral suppression during the first 24 months after initiating ART. In the univariate proportional hazard regression, we observed no significant association between any baseline characteristics and virologic failure (Table B in [S1 File](#)). In the multivariable proportional hazard regression, lower risk of

Table 1. Cohort descriptive characteristics.

Characteristic	Category	All Participants N = 559	Women N = 386	Men N = 173	P value
Age (years)	< 30	127 (23%)	104 (27%)	23 (13%)	0.001
	30–40	280 (50%)	189 (49%)	91 (53%)	
	> 40	152 (27%)	93 (24%)	59 (34%)	
	Median (IQR)	35 (30–41)	33 (29–40)	38 (33–42)	
Formal education level	None or any primary	257 (46%)	197(51%)	60 (35%)	<0.001
	Any secondary	232 (42%)	153 (40%)	79 (46%)	
	Any post-secondary	70 (13%)	36 (9%)	34 (19%)	
Employment	Unemployed	272 (49%)	204 (53%)	68 (39%)	<0.001
	Self-employed	142 (25%)	103 (27%)	39 (23%)	
	Gov't or organization	77 (14%)	38 (10%)	30 (17%)	
	Private employer	68 (12%)	41 (10%)	36 (21%)	
Household income	No income	184 (33%)	136 (35%)	48 (28%)	<0.001
	Income >1 US\$/day	194 (35%)	156 (40%)	38 (22%)	
	Income < 1 US\$/day	181 (32%)	94 (24%)	87 (50%)	
Housing material	Mud	187 (33%)	124 (32%)	63 (36%)	0.32
	Brick	372 (67%)	262 (68%)	110 (64%)	
CD4 count*	< 100	292 (53%)	196 (51%)	96 (56%)	0.09
	100–200	185 (33%)	132 (35%)	53 (31%)	
	> 200	76 (14%)	53 (14%)	23 (13%)	
	Median (IQR)	98 (21–163)	100 (29–170)	87 (13–152)	
Physical functional ability	Impaired (Karnofsky <80)	189 (34%)	126 (33%)	63 (36%)	0.38
	Not impaired	370 (66%)	260 (67%)	110 (64%)	
10-year mortality	Dead	127 (23%)	86 (22%)	41 (24%)	0.71
	In care or left cohort	432 (77%)	300 (78%)	132 (76%)	
10-year viral failure^a	Viral failure	107 (29%)	75 (30%)	32 (28%)	0.81
	No failure	365 (71%)	250 (70%)	115 (72%)	

Values are N(%) or median (interquartile range). *P*-value testing for gender differences in characteristics was done using the chi-square test

*Baseline CD4 count was available for 553 participants

^a10-year viral failure was available for 472 participants

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virologic failure was significantly associated with age >40 years and self-employment compared to unemployment (hazard ratio, 0.60; 95%CI, 0.37–0.98). Any regular household income <1 USD/day (hazard ratio, 1.81; 95% CI 1.10–2.98) and regular income >1 USD/day (hazard ratio, 2.33; 95%CI 1.24–4.39) were both associated with higher risk of treatment failure compared to participants with no regular household income in multivariable analysis.

Composite outcome (mortality or virologic failure)

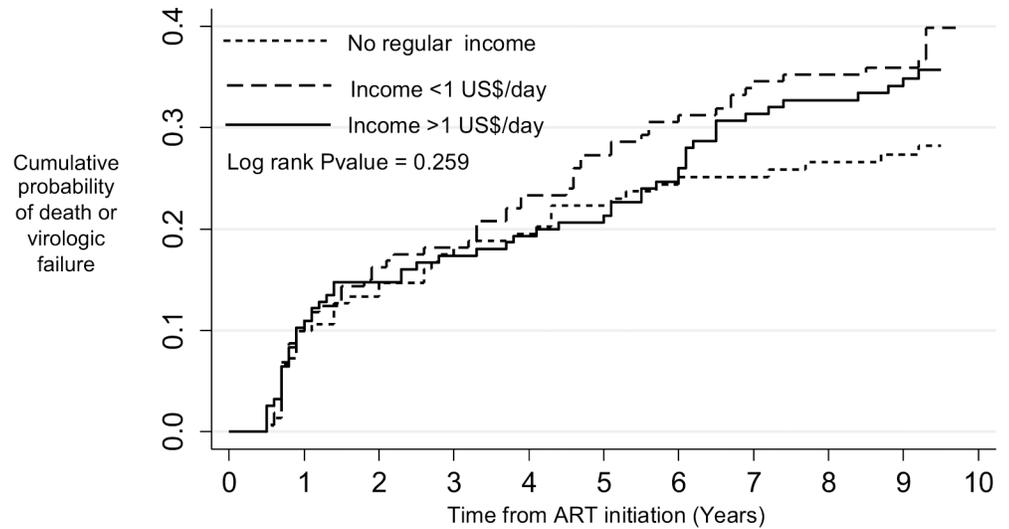
In Kaplan-Meier survival analysis cumulative probability of death or treatment failure was not significantly different when participants were grouped by baseline characteristics (Fig 1). When viewing death or viral failure together as a composite outcome in the univariate proportional hazard regression, Karnofsky score >80 was significantly associated with lower risk of the combined outcome (Table 2). In the multivariable regression, the composite outcome was significantly positively associated with any regular household income <1 USD/day (hazard ratio, 1.88; 95%CI 1.23–2.87) and with regular household income >1 USD/day (hazard ratio, 2.18; 95%CI 1.27–3.74) compared with no regular household income. Compared to unemployment, self-employment was significantly associated with decreased risk of the composite outcome of death or viral failure (hazard ratio, 0.59; 95%CI 0.38–0.92). To account for the possibility that participants lost to follow-up were not missing at random, we repeated the Cox regression with loss to follow-up included in the composite outcome. We did not observe any significant differences in the unadjusted or adjusted results.

Discussion

Our study is among the first to examine socioeconomic position and long-term ART outcomes in Africa. Employment and household income may be related to ten-year survival and viral suppression among individuals receiving ART in this setting. Employment status was found to be significantly associated with cumulative probability of death in Kaplan-Meier analysis, with unemployed participants experiencing death at the highest rate. Subsequently a clear significant relationship was identified between self-employment and lower incidence of the combined death and viral failure outcome when compared to unemployment in the adjusted Cox regression, after controlling for known confounding covariates such as physical disability. Although this data and methodology cannot ascertain causality, these observations suggest that unemployment may be a risk factor for long-term adverse ART outcomes, which supports similar findings in the literature on shorter ART outcomes in sub-Saharan Africa.[27, 38]

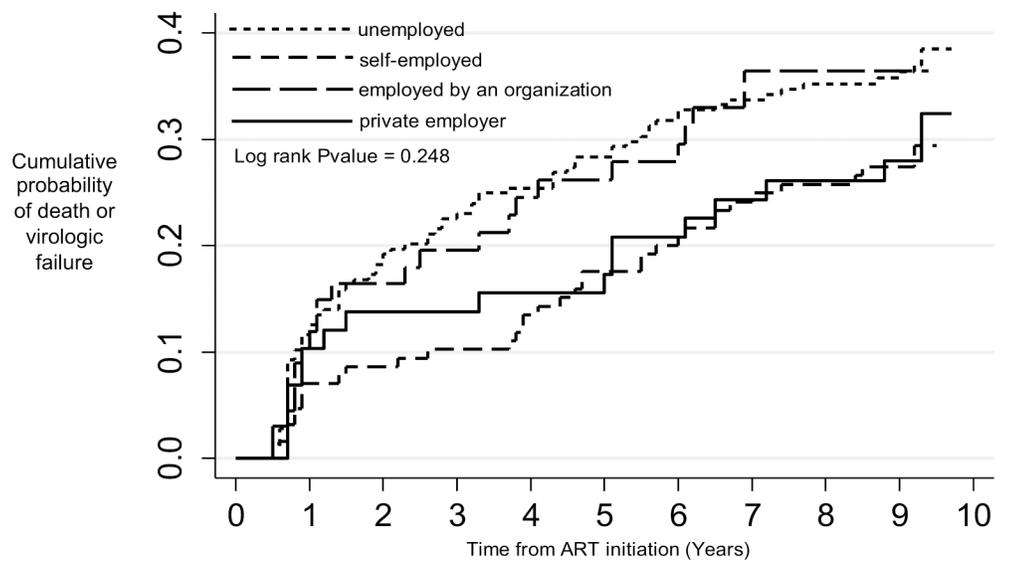
In our cohort data, household income was largely separate from employment status because it measured the contributions of all household members. Any association between household income and the mortality/viral failure endpoint was not strong enough to reach significance in Kaplan-Meier analysis or unadjusted Cox regression. However, clear significant relationships were identified in the adjusted model between higher household income and higher incidence of the composite outcome (death or viral failure). The measure of higher household income, separate from employment status, may have captured a risk factor related to decreased adherence and poor outcomes. Of note, the cohort subset with income >1USD/day, which exhibited the highest relative rate of viral failure, also had the highest self-reported medication adherence. Further research is needed to better understand the interplay between household income and ART outcomes.

Substantial variation in the cohort's socioeconomic characteristics provided enough diversity to test for outcome differences. The long follow-up period with rigorous outcome ascertainment and low loss-to-follow-up of 6% also contribute to the results' validity. Our inclusion of baseline CD4 count and functional impairment in the analysis enabled us to avoid the potential confounding of clinical status at the time of ART initiation. The different associations observed between various socioeconomic characteristics and outcomes reinforces the finding that socioeconomic position consists of separate factors that have distinct relationships with health and healthcare. Of note, formal education level was found to be unrelated to ten-year incidence of mortality or virologic failure. This finding is encouraging to HIV providers and ART programs serving populations with low levels of formal education. The ratio of women to



No regular income	152	133	126	120	117	111	106	104	98	86
<1 USD/day	163	144	132	128	117	110	105	99	94	87
>1 USD/day	156	140	132	125	121	118	113	102	99	87

Number at risk



Unemployed	218	187	171	162	156	147	138	133	125	113
Self-employed	128	118	114	112	106	100	98	92	90	81
Employed by organization	58	52	50	50	48	48	45	43	40	34
Privately employed	67	60	55	49	45	44	43	37	36	32

Number at risk

Fig 1. Death or virologic failure among HIV-infected participants surviving more than six months on ART grouped by household income and by participant employment status (N = 472). Caption: Fig 1A shows a trend

towards increased risk of death and viral failure among participants with higher regular household income, while Fig 1B shows a trend towards decreased risk of death and viral failure among self-employed and privately employed participants. The multivariable proportional hazard regression identified a significant positive association between higher household income and higher incidence of the composite outcome and a significant association between self-employment and decreased incidence of the composite outcome compared with unemployment.

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men in this cohort represented the ratio of women and men enrolled at the Infectious Diseases Institute and in the country, likely due to higher HIV prevalence in women and more HIV screening in women, especially during antenatal care. We observed significant socioeconomic differences between women and men. However, we found no significant association between sex and any outcome, leading to the conclusion that sex alone was not predictive of survival or viral failure.

Existing literature widely encourages socioeconomic interventions for HIV patients [5, 26, 31, 39] and some HIV programs have implemented such interventions.[32] Our findings suggest efforts to boost employment among people living with HIV and receiving ART may promote successful long-term disease control. The Infectious Diseases Institute clinic provided routine support to all patients in this cohort, including counseling, telephone calls to schedule visits and after missed visits and one-on-one provider-patient encounters. Financial support

Table 2. Risk factors for 10-year mortality or virologic failure (combined outcome) in a Ugandan cohort with baseline AIDS receiving ART (N = 472).

Baseline Category	Baseline Characteristics	Unadjusted Hazard Ratio (95% CI)	P value	Adjusted Hazard Ratio (95% CI)*	P value
Sex	Men	0.95 (0.67–1.34)	0.76	0.82 (0.56–1.20)	0.30
Age, years	< 30	1.00	Ref	1.00	Ref
	30–40	0.73 (0.49–1.08)	0.11	0.80 (0.53–1.21)	0.29
	> 40	0.97 (0.64–1.48)	0.90	0.95 (0.61–1.48)	0.82
Highest education level	Primary	1.00	Ref	1.00	Ref
	Secondary	1.22 (0.88–1.70)	0.24	1.24 (0.87–1.76)	0.23
	Tertiary	0.81 (0.45–1.43)	0.46	0.76 (0.40–1.45)	0.40
Employment status	Unemployed	1.00	Ref	1.00	Ref
	Self-employed	0.70 (0.47–1.03)	0.07	0.59 (0.38–0.92)	0.02
	Organization/Govt	0.97 (0.61–1.54)	0.89	0.83 (0.45–1.53)	0.56
	Privately employed	0.73 (0.43–1.23)	0.24	0.58 (0.31–1.09)	0.09
Household income	No regular income	1.00	Ref	1.00	Ref
	Income <1 US\$/day	1.38 (0.93–2.06)	0.11	1.88 (1.23–2.87)	<0.01
	Income >1 US\$/day	1.27 (0.85–1.91)	0.24	2.18 (1.27–3.74)	<0.01
Physical housing	Brick house	1.00	Ref		
	Mud house	1.00 (0.72–1.40)	0.99		
Karnofsky Score	Karnofsky ≥80	0.67 (0.48–0.93)	0.02	0.74 (0.52–1.05)	0.09
CD4 count/μL	<100	1.00	Ref		
	100–200	0.79 (0.55–1.12)	0.18	1.02 (0.70–1.48)	0.94
	>200	0.86 (0.54–1.37)	0.52	1.07 (0.65–1.75)	0.79
Time-varying characteristics	Karnofsky ≥80	0.10 (0.06–0.17)	<0.001	0.52 (0.42–0.65)	<0.001
	CD4 <100	1.00	Ref	1.00	Ref
	CD4 100–200	0.31 (0.19–0.52)	<0.001	0.50 (0.39–0.64)	<0.001
	CD4 >200	0.09 (0.05–0.15)	<0.001	0.36 (0.29–0.56)	<0.001

Hazard Ratio calculated via Cox proportional hazard model and *adjusted for sex, age, education, employment, income, baseline and time-varying Karnofsky and CD4

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for transport—a leading barrier to patient retention in Uganda [40]—was given four times per year with quarterly disbursements between USD 2.00 and 2.60. Ten-year viral suppression in our Ugandan cohort was similar to high-income countries [41] and should be encouraging to policymakers and program administrators seeking to reduce mortality and achieve viral suppression in socioeconomically diverse HIV-infected populations in low-income countries.

Several limitations of our data collection and analysis are worth mentioning and merit further research. Although we used broad categories to measure socioeconomic variables, limitations exist with patient self-reported information. Our baseline measurement of socioeconomic position upon enrollment is a common method and may be sufficient for assessing relatively static characteristics such as education and housing material in adults. [6, 9, 28] However, the single measurement represents a significant limitation and further research may benefit from a time-varying measurement of employment and income as they change during years of treatment. Our measurements of household income placed participants in only three categories and did not account for household size or for barriers affecting adherence, such as social stigma and work or schedule barriers to regular ART that may help to explain an association between higher household income and poor outcomes. Although our measure of functional impairment with the Karnofsky performance status test adds an important component to our analysis, the Karnofsky scale is a relative blunt tool. Further research may benefit from more detailed measures of cognitive or physical impairment. Kaplan-Meier and univariate proportional hazard regression methods of testing for predictive associations between socioeconomic characteristics and outcomes allow for straightforward interpretation of coefficients, although our data only allows tests for association, not causality. These adjusted hazard ratios provide additional information but must be interpreted with caution. Lastly, the resources available to our clinic were more than those available to most public sector clinics in low-income countries. Without sufficient clinic resources, lower socioeconomic position may emerge as a more prominent contributor to poor outcomes of patients on ART.

Supporting information

S1 File. Table A. Risk factors for all-cause 10-year mortality in a Ugandan cohort with baseline AIDS receiving ART (N = 559). Table B. Risk factors for 10-year virologic treatment failure in a Ugandan cohort with baseline AIDS receiving ART (N = 472). (DOCX)

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Author Contributions

Conceptualization: Andrew G. Flynn, Agnes N. Kiragga, Moses Kamy, David B. Meya, David R. Boulware, Andrew Kambugu, Barbara C. Castelnuovo.

Data curation: Godwin Anguzu, Frank Mubiru, Agnes N. Kiragga, Moses Kamy, Andrew Kambugu, Barbara C. Castelnuovo.

Formal analysis: Andrew G. Flynn, Godwin Anguzu, Frank Mubiru, Agnes N. Kiragga, Barbara C. Castelnuovo.

Funding acquisition: Andrew G. Flynn, Moses Kanya, David B. Meya, David R. Boulware, Andrew Kambugu, Barbara C. Castelnovo.

Investigation: Andrew G. Flynn, Godwin Anguzu, David B. Meya, David R. Boulware, Andrew Kambugu, Barbara C. Castelnovo.

Methodology: Andrew G. Flynn, Frank Mubiru, Agnes N. Kiragga, David R. Boulware, Barbara C. Castelnovo.

Project administration: Andrew G. Flynn, Barbara C. Castelnovo.

Resources: Moses Kanya, David B. Meya, David R. Boulware, Andrew Kambugu, Barbara C. Castelnovo.

Software: Godwin Anguzu, Frank Mubiru, Agnes N. Kiragga.

Supervision: Andrew G. Flynn, Frank Mubiru, Agnes N. Kiragga, David B. Meya, David R. Boulware, Andrew Kambugu, Barbara C. Castelnovo.

Visualization: Godwin Anguzu.

Writing – original draft: Andrew G. Flynn, Godwin Anguzu, Agnes N. Kiragga, David B. Meya, David R. Boulware, Barbara C. Castelnovo.

Writing – review & editing: Andrew G. Flynn, Agnes N. Kiragga, David R. Boulware, Barbara C. Castelnovo.

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