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Interventions to mitigate the impact of HIV infection in key populations in sub-Saharan Africa

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Interventions to mitigate the impact of HIV infection in key populations in sub-Saharan Africa

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Dedication

To my happy-always daughter Alaine Elizabeth Atuhaire.

To my beloved nephew Ayebare Primo.

Life and the universe will be kind to you always.

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Data sources

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Contributions

The following individuals assisted in one way or another with conceptualization of the studies that make up this dissertation, as well as with data collection and writing and editing of the resulting scientific papers.

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Interventions to mitigate the impact of HIV infection in key populations in sub-Saharan Africa

Stephen Bambeiha Asiimwe

Abstract

In sub-Saharan Africa (SSA), the region with the world's highest HIV prevalence, antiretroviral therapy (ART) has recently reduced AIDS-related deaths. However, death rates still remain unacceptably high, as do the numbers of new HIV infections. HIV treatment is also often provided by stand-alone HIV clinics, distinct from other healthcare services. As the people living with HIV (PLWH) start to survive into older age, adequately addressing emerging challenges, including but not limited to age-related diseases and disabilities, will require more integration for HIV- and non-HIV services. Whereas ART, especially early ART for all HIV-infected patients, is the single most important intervention against HIV-related mortality and morbidity, the persistence of some complications (e.g., HIV-associated neurocognitive disorder [HAND]) and high rates of residual mortality in the ART era suggest that additional interventions are needed.

In the first chapter of my dissertation, I present a comparison of the cognitive scores of PLWH in a rural community in South Africa and HIV-negative comparators in the same community. Although adverse cognitive outcomes have been reported in clinical studies PLWH, no prior population-based studies in SSA have compared cognitive functioning among PLWH and HIV-negative comparators. The baseline data of participants in the "Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa" (HAALSI), a population-based cohort in rural Agincourt, Mpumalanga, northeast South Africa, were analyzed. Participants, who are men and women aged at least 40 years. Cognitive scores on a conventional instrument assessing orientation, immediate and delayed recall, and numeracy for 4,560 participants, and a novel instrument (the Oxford Cognitive Screen [OCS]-Plus), assessing memory, language, visual-spatial ability, and executive functioning for 1,997 participants were used to measure cognitive functioning. We used linear regression to compare composite cognitive scores between PLWH and HIV-negative participants, and among PLWH, anti-retroviral therapy (ART) users

versus non-users. Multilevel (random-intercepts) linear models assessed domain-specific associations on the OCS-Plus. Estimates were adjusted for age, gender, education, country of birth, father's occupation, household asset index, and ever-consumed alcohol. Of 4,560 participants, 1,048 were HIV positive (719 used ART). PLWH averaged 0.06 (95% CI: 0.01 to 0.12) standard deviation units higher scores on the conventional cognitive battery than HIV-negative participants. However, PLWH averaged 0.03 (95% CI, -0.08 to 0.03) standard deviation units lower scores on the OCS-plus instrument, the result not reaching statistical significance. Among PLWH, ART use did not predict cognition. There were no domain-specific cognitive effects from HIV or ART using the OCS-Plus measures. PLWH thus had higher cognitive function scores than HIV-negative comparators on a conventional cognitive assessment but not on a novel measure designed for low-literacy settings.

In the second chapter, I present an assessment of the association between HIV status and ART and age-related disability in the HAALSI baseline sample. We specifically evaluated whether these associations depend on body mass index (BMI). Although antiretroviral therapy (ART) use could mitigate risk of age-related disability among people living with HIV (PLWH), ART often causes weight-gain and could counter-intuitively increase risk of disability through elevated BMI. The baseline data of 4552 individuals (1040 with HIV and 3512 without HIV) were analyzed. Primary predictors were HIV status and ART use. The outcome was disability in at least one of five basic ADLs (walking across the room, getting up from bed, dressing, bathing and using the toilet). BMI, calculated from measured weights and heights, was considered in categories of underweight ($<18.5 kg/m^2$), normal BMI (18.5 to <25), overweight (25 to <30) and obese (≥30). We estimated prevalence differences in the outcome comparing PLWH to participants without HIV, and among PLWH, ART users to non-users. Additional models in PLWH compared virally suppressed ART users vs. unsuppressed ART users vs. ART non-users. We assessed BMI effects using its interaction with HIV and ART use. All regression models were adjusted for age and sex; more comprehensively adjusted models added education, father's occupation, country of origin, and alcohol use. Among the 4552 study participants, 11.9 % reported at least one ADL disability.

PLWH had lower prevalence of obesity (21% among PLWH vs 30% in participants without HIV) but higher prevalence of underweight (7.4% among PLWH vs 4.6% among participants without HIV). Among PLWH, those who were underweight had 13.3 percentage points (95% CI: 3.8 to 22.8) higher prevalence of an ADL disability than those with normal BMI. Those with obesity had 2.9 percentage points (95% CI: -2.3 to 8.1) higher prevalence of an ADL disability than those with normal BMI, the result not reaching statistical significance. Among the 69% of PLWH who were ART users, those with underweight had 13.7 percentage points (95% CI: 2.8 to 24.4) higher prevalence of ADL disability than normal-weight ART users. Those with obesity had 1.2 percentage points higher prevalence of an ADL disability (95% CI: -4.3 to 6.9) higher prevalence of an ADL than those with normal BMI, the result not statistically significant. Underweight participants thus had increased prevalence of ADL disability, but overweight and obese individuals did not. We find no evidence that weight increases associated with ART use are likely to increase disability.

In the third and final chapter, I assess the sufficiency of ART in eliminating excess mortality from Kaposi's sarcoma (KS), an HIV-associated cancer, among HIV-infected adults initiating ART in Uganda. Despite KS being among the most common adult malignancies in the region following the onset of the HIV epidemic, approaches to its therapeutic management have largely been extrapolated from high-resource settings such as the US. In particular, antiretroviral therapy (ART) is often used alone for the initial management of persons with KS who do not have immediately life-threatening complications without any direct evidence in African patients of the effectiveness of this strategy. Among HIV-infected participants in Uganda who were initiated on ART, we compared those with biopsy-confirmed KS to those without KS. We used a directed acyclic graph (DAG) to identify relevant confounders, which were measured identically in both groups, in order to test the hypothesis that the participants with KS have excess mortality. Survival was determined over 4 years with dedicated attention to decrease loss to follow-up by actively tracking lost participants in the community. We evaluated 224 participants with KS and 683 participants without KS who were initiated on ART between 2005 and 2013. Males were 37%,

median values were; age 34 (IQR 28 to 40), CD4+ T-cell count 158 cells/mm^3 (IQR 76 to 263), and plasma HIV RNA level 5.2 $\log_{10}$copies/ml (IQR 4.6 to 5.6). In the unadjusted analysis, mortality at 1 year was 18.8% in those with KS and 3.9% in those without KS; at 4 years, mortality was 30.4 % and 8.2% respectively. After adjustment using proportional hazards regression for age, sex, asset holding, history of tuberculosis, history of cryptosporidial diarrhea, history of esophageal candidiasis, physical health summary score, body mass index, hemoglobin, CD4+ T cell count, plasma HIV RNA level, and calendar date of ART initiation, participants with KS had a 5.0-fold (95% CI 2.5-10.0; $p < 0.001$) higher rate of death in the first year after start of ART than those without KS and a 2.9-fold (95% CI 1.2-7.0, $p=0.020$) higher rate of death thereafter. In a prototypical patient, the absolute difference in risk of death among those with KS +20% at 4 years. Even in this population of patients with KS who did not have immediately life-threatening complications, use of ART alone did not eliminate excess mortality from KS.

The findings of this work do suggest the need for additional interventions over and above ART to address HIV-related morbidity and mortality in SSA. We did not find evidence that PLWH are likely to have increased burden of cognitive impairment or disability. However, future studies should explore cognitive and disability trajectories in longitudinal data to further evaluate associations with HIV and ART use, especially early ART, to guide intervention.

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Chapter 1 : Cognitive differences associated with HIV serostatus and antiretroviral therapy use in a population-based sample of older adults in South Africa

Background

Despite the now widespread use of antiretroviral therapy (ART) among people living with HIV (PLWH), HIV-associated neurocognitive disorder (HAND) remains a prevalent HIV-related complication [1]. HAND is sub-classified according to its progression as asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), or HIV-associated dementia (HAD) [2]. In the US, estimates of cumulative incidence of MND in ART-treated PLWH approximately one year after ART initiation ranged from 16% to 21%, and were higher than estimates of similar neurocognitive disorder in HIV-negative individuals [3, 4]. Previous clinical studies in South Africa reported high prevalence of HAND among PLWH, ranging from 53% [5] to 67% [6]. However, there is no prior population-based study comparing neurocognitive impairment among PLWH (ART users and non-users) and HIV-negative comparators in sub-Saharan Africa (SSA) [7].

The high burden of HAND in the ART era suggests that interventions over and above ART may be required to address the problem. However, ART is now available in the public health sector for most of SSA [8, 9], and its effects on cognition in HIV-affected populations ought to be investigated directly. Studies from high-income countries suggest persistence of cognitive impairment in the ART era at rates comparable to those in the pre-ART era. However, some studies suggest change in presentation from predominantly motor skills, cognitive speed, and verbal fluency impairment in the pre-ART era, to predominantly memory and executive function impairment in the ART era, suggesting possible domain-specific effects from HIV and/or ART [10]. Even if ART does not influence cognition overall, identifying domain-specific effects of HIV and/or ART on cognition may advance our understanding of the mechanisms of cognitive impairment, potentially guiding clinical care and future research.

The context may also modify the effects of HIV and ART on cognition. For example, in SSA, PLWH often begin ART with severe levels of immunosuppression [11]. Such biological characteristics – as well as a wide range of socio-structural characteristics (e.g., social-support)– could lead to different

distributions of HAND in SSA setting compared to other contexts, and possibly different impacts from ART [12].

Measurement of cognitive function is challenging in SSA. Conventional cognitive performance tests developed for high-literacy settings, may not be appropriate in low-literacy settings [13, 14]. Previous work in the "Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa" (HAALSI) has thus developed a novel tablet-based cognitive performance instrument, the Oxford Cognitive Screen (OCS-Plus), designed to be more appropriate for a low-literacy setting. Unlike most conventional tests, which rely on language and numeracy skills, the OCS-Plus instrument relies more on visual and auditory abilities [15, 16].

We used HAALSI baseline data to describe in a cross-sectional analysis the population distribution of cognitive outcomes in a community of older PLWH residing in SSA. Our specific aims were to: (i) compare the cognitive performance of PLWH and HIV-negative comparators; (ii) among PLWH, compare cognitive performance between ART users and non-users, and (iii) evaluate the performance of specific cognitive assessment instruments. We hypothesized that: (i) PLWH would have lower overall cognitive scores due to negative effects of HIV on cognitive performance; (ii) among PLWH, ART users would have higher scores due to beneficial effects of ART on cognitive performance; (iii) the associations of HIV and ART with cognition would vary between the conventional and the novel OCS-Plus measures; and iv) the associations of HIV and ART with cognitive scores would also vary across different domains of the OCS-Plus measure.

Methods

Sample

Participants were part of the HAALSI cohort, a population-based study designed to measure the health and well-being of adults 40 years and older in the rural Agincourt sub-district, Mpumalanga province, northeast South Africa [16]. HAALSI participants were sampled from the 2013 census round of the

existing MRC/Wits-Agincourt Health and socio-Demographic Surveillance System (HDSS), which is part of the International Network for the Demographic Evaluation of Populations and their Health (INDEPTH) [17]. The HAALSI study enrolled 5,059 men and women who were 40 years or older on July 1, 2014 [17-19]. For this analysis, we restricted our sample to 4,582 participants who provided dried blood spots and consented to HIV tests. We excluded participants who had indeterminate HIV test results (N = 22) and HIV-positive participants whose treatment status could not be established (N = 8) and analyzed 4,560 individuals (90% of the original 5,059 HAALSI participants) (**Figure 1.1**).

Given the prevalence of low-literacy in the sampled population, about half of HAALSI participants were randomly selected to participate in a novel cognitive function assessment, the OCS-plus instrument, which was designed for use in low-literacy settings [15]. Sampling for completion of this assessment was stratified by age and sex to allow appropriate representation.

Predictor measurement

HIV-infection was assessed using PCR tests on dried blood spots (DBS) (Vironostika Uniform 11, Biometrica, France). Viral load measurements (Biomeriux NucliSens, Durham, NC, USA) were performed on those testing HIV-positive. DBS samples for those testing HIV-positive were also tested for emtricitabine (FTC) and lamivudine (3TC). PLWH typically receive either FTC or 3TC but not both of these commonly used antiretroviral drugs [16, 18]. We regarded all HIV-positive individuals who were either virally suppressed or positive on any antiretroviral drug as ART users. PLWH who were virally suppressed but negative for antiretroviral drugs (N=52) were classified as ART users; we did not believe that such individuals would be suppressed for reasons other than ART [20].

Outcome measurement

For the conventional cognitive function measure, a previously constructed score assessing orientation, memory, and numeracy was used [21]. Orientation assessed: current year, month, date, and South African president (4 points). Memory assessed immediate word recall (list of 10 words in xiTsonga, the

local language, read out by the interviewer), and delayed word recall (read from the same 10-word list after 4 to 5 minutes of unrelated questions) (20 points). Numeracy assessed ability to count from 1 to 20 (forward counting) (1 point). Those able to count were further asked to complete the fourth digit of the sequence 2, 4, 6, ... (1 point). Scores were combined into a z-standardized latent variable via confirmatory factor analysis in Mplus [21, 22].

Nearly half of the participants in this older-age community-representative sample were illiterate. We thus explored the novel Oxford Cognitive Screen (OCS)-plus measures, intended to be more appropriate than conventional batteries in low-literacy settings, in a randomly selected smaller sample [15].

We used 10 items from the OCS-Plus measures, designed to tap into distinct cognitive domains and minimize education- and literacy-related bias. Previous (unpublished) factor analyses of the OCS-plus data in HAALSI suggested 4 underlying factors: memory, language/semantic knowledge, visuospatial ability and executive function. The memory domain included a 5-word immediate recall task, delayed word recall (4-5 minute delay), and delayed word recognition, which tested ability to recognize words not retrieved during free recall (3 items, 5 points each).

The language domain was measured by a picture naming task with 4 low-frequency target pictures; and a test of semantic knowledge (4 objects), requiring participants to point to a particular object or identify the object from a specific semantic category (2 items, 4 points each).

The visuospatial domain included two tests of constructional praxis. In one test, the respondent was asked to use a stylus to copy a complex object presented on the tablet screen (figure copy). In another test, the object was briefly presented on the screen (2 seconds), and the respondent was asked to draw it from memory (figure recall). In each test, the object had 7 defining elements, each scored for presence (1 point), accuracy (1 point) and position (1 point) (2 items, 21 points each).

The executive function domain consisted of three different versions of a non-verbal trails task, where respondents were asked to connect shapes on the tablet screen using different rules (a point for each

correct connection, 7 points maximum): first circles small to large, then squares large to small, and then alternating between circles and squares, decreasing in size for squares and increasing in size for circles (3 items, 7 points each).

Covariate measures

We represented our assumptions regarding the underlying causal structure using a directed acyclic graph (**Figure 1.2**) in order to guide the selection of covariates into our regression models. Covariate data collected during in-person interviews included father's main occupation (manual labor vs. services vs. self-employed or business owner vs. professional vs. others), country of birth (South Africa vs. Mozambique or other), sex (male vs. female), age (years), education (no formal education vs. some primary education vs. some secondary education vs. secondary or more), ever consumed alcohol (yes vs. no), and asset index score (z-standardized score representing asset ownership, household quality and energy sources) [23]. As cardiovascular risk factors such as hypertension could also mediate effects of HIV and ART on cognition [18], we measured systolic blood pressure (SBP) and diastolic blood pressure (DBP). Three measurements were taken two minutes apart with an electronic BP machine and the necessary cuff depending on the size of the participant (Omron, Kyoto, Japan). The average from the last two measurements was used [16, 18].

Analyses

Descriptive analyses

We assessed the distributions of scores on each cognitive instrument comparing PLWH to HIV-negative individuals, and in PLWH comparing participants currently using ART to those not using ART.

The associations of HIV and ART use with cognitive function using conventional measures

We used linear regression to predict scores on the conventional cognitive function battery with HIV status as the predictor. We repeated this analysis using ART as the predictor, restricting to PLWH. We controlled for two sets of covariates: *model 1* included age, sex, country of birth, father's occupation,

education, asset index, and alcohol consumption; *model 2* additionally included SBP, DBP, and – when evaluating effects of ART – log-transformed viral load.

Derivation of domain-specific measures from the OCS-Plus instruments

We used R's Lattice package to estimate and extract z-standardized factor scores representing the four cognitive function domains of memory, language, visuospatial ability, and executive functioning from the ten individual OCS-Plus cognitive test items (**Figure 1.3**) [24].

Cognitive domain-specific effects of HIV and ART use

To evaluate possible domain-specific effects from HIV/ART on cognition, we used a multi-level model (**Equation 1**) treating domain-specific z-scores on OCS-Plus instruments as distinct measures of cognitive function clustered within individuals. The model nested multiple cognitive assessments within individuals predicting each cognitive z-score outcome with indicator variables for each cognitive domain (memory, language, visuospatial ability, and executive functioning) and an interaction between these domains and the primary predictor (HIV or ART). Numeric covariates were centered at their means.

Specifically, letting Y_{ij} represent cognitive z-score of individual i on domain j, we estimated multilevel models such as (using the ART use exposure model as the example):

$$Y_{ij} = \beta_{00} + \Sigma\beta_1 M_{ij} + \beta_2 A_i + \beta_3 C_i + \Sigma\beta_4 A_i * M_{ij} + \mu_{0i} + \varepsilon_{ij} \quad (1)$$

In this model, β_{00} would represent average score on the reference cognitive domain (which we specified as memory in all models) among ART non-users in the reference categories of categorical covariates with the mean values of numeric covariates. M_{ij} is a set of indicator variables representing the four cognitive function domains, and β_1 represents the corresponding coefficients (deviations from mean score in the reference outcome of memory for each cognitive domain in ART non-users); because we estimated 4 domains, there are 3 indicator variables and corresponding coefficients, which we suppress in equation 1. A is an indicator variable for treatment status and β_2 is the estimated effect of ART on memory, β_3 represents coefficients for confounders, and β_4 represents the set of coefficients indicating the differential

effect of ART on a given cognitive domain; these coefficients test the hypothesis that the effects of ART differ across cognitive domains. Error terms μ_{0i} (representing random variability between individuals) and ε_{ij} (representing random variability within individuals) were assumed to be approximately normally distributed.

Interaction between age and HIV in their association with HIV

As age is strongly associated with cognitive function, we assessed for its interaction with HIV in predicting cognitive scores on the conventional measure and a simple average of the 4 domain-specific z-standardized scores on the OCS-Plus instrument.

Missing data

For the analysis using the conventional measure of cognitive function, we conducted a complete-case analysis (only 92/4582 (2%) of participants had missing scores and less than 1% of participants were missing any covariate data). Missing data in specific items on the OCS-Plus measure ranged from 0.8% on picture identification to 32% on figure copy. We used multiple imputation to impute missing values on the OCS-Plus variables before confirmatory factor analysis and subsequent analyses. Multiple imputation was implemented using the MICE package in R [25]. We used predictive mean matching to estimate missing values based on 5 nearest neighbors and created five copies of the dataset with missing values imputed under a missing-at-random assumption given a participant's age, gender, education, asset index, country of origin, HIV test results, systolic blood pressure, diastolic blood pressure, alcohol ever consumption, and father's occupation. Subsequent analyses were performed on each of the imputed datasets and results pooled into a final estimate [26, 27].

Results

Sample characteristics

The HIV prevalence among those tested was 1040/4582 (23%). PLWH were younger on average than HIV-negative participants (55 years [SD=10] vs. 64 years [SD = 13]), had slightly lower formal education

(41% vs. 47%), slightly lower systolic blood pressure mean = 130 (SD = 22) versus 140 (SD = 23) mmHg, and lower average score on the wealth and asset index, -0.31 (SD = 2.2) vs. 0.1 (SD = 2.4) (**Table 1.1)**. Among the 1040 PLWH analyzed, 719 (69%) were ART users. The ART users were like non-ART users with respect to all covariates except they presented with a much lower viral load (mean = 5874 copies/ml, SD = 22610, in ART users versus 52300, SD = 250269 among non-ART users) (**Table 1.1**).

Distributions of cognitive function measures

PLWH had higher mean scores on the conventional cognitive function battery than HIV-negative participants. The OCS-Plus scores were similar between groups except for trail tests, where PLWH had slightly higher scores (**Table 1.2**).

Association of HIV status and ART treatment with cognitive scores on the conventional measure

After adjustment for confounders, PLWH had slightly higher cognitive z-scores than HIV-negative participants on the conventional cognitive battery ($\beta = 0.06$; 95% CI, 0.01 to 0.12). Additional adjustment for systolic blood pressure and diastolic blood pressure did not significantly alter the results (**Table 1.3**). For context, in this sample a 1-year age increase was associated with a cognitive score difference of -0.021 (95% CI, -0.018 to -0.023).

Among PLWH, we did not find evidence for significant differences in cognitive score by ART use status. In a sensitivity analysis comparing PLWH using ART and PLWH not using ART to HIV negative individuals, there were no significant differences in cognitive scores between ART users and non-users, although both groups had higher scores on the conventional measure than HIV-negative individuals (**Table 1.4**).

Association of HIV infection with cognitive function on the OCS-plus instrument

In the multi-level model adjusting for covariates, there were no significant domain-specific interactions for the effects of HIV on cognition (**Table 1.5**). In a model to estimate the overall effect of HIV and ART

on cognition using the OCS Plus instrument (dropping the measure by exposure interaction), PLWH had slightly lower cognitive scores than HIV-negative participants, although the result was not statistically significant (β = -0.03; 95% CI, -0.08 to 0.03). Among PLWH, ART users had higher cognitive scores than non-ART users, but the confidence interval was wide and included the null (β = 0.05; 95% CI, -0.05 to 0.15) (**Table 1.5**). Similar findings were observed in additional models, where the outcome was a simple average of the scores on the 4 OCS-Plus domains (**Table 1.6**).

Interaction between age and HIV in their association with cognitive score

In the analysis using the conventional measure, older PLWH had higher cognitive scores than older participants without HIV (**Figures 1.4 and 1.5**). In a model to predict scores on the conventional cognitive function measure, adjusting for covariates, and including an interaction term between centered age and HIV status, PLWH had higher overall cognitive scores (β = 0.11, 95% CI, 0.05 to 0.18) and the age-slope was slightly flatter (β = 0.01, 95% CI, 0.004 to 0.014). In a similar model using the average of scores on the 4 OCS-Plus domains as the outcome, PLWH averaged lower scores on (β = -0.078, 95% CI, -0.14 to 0.001), though the result did not reach statistical significance, and there was no interaction between age and HIV status (β =-0.01, 95% CI, -0.01 to 0.001) (**Table 1.7**).

Discussion

This study presents, for the first time to our knowledge, a comparison of the cognitive function in older people by HIV status in SSA. The comparison was done in groups with similar sociodemographic characteristics, in an HIV hyperendemic community in rural South Africa. We observed higher overall cognitive function scores among PLWH when cognition was measured by a conventional battery of questions commonly used in high-income countries. However, we did not observe differences in cognition when function was measured using the OCS-Plus instrument, which uses visual and auditory cues to minimize literacy-related bias in cognitive testing in low-literacy communities [18]. ART use was non-significantly associated with better cognitive outcomes among PLWH.

The finding that PLWH presented with higher overall cognitive function by the conventional battery was surprising. Most prior evidence suggests that PLWH average lower cognitive function scores presumably because of adverse effects from HIV infection on cognition. In a US study, older PLWH had slightly higher cumulative incidence of MND (5% vs. 3%) compared to HIV-negative participants [4]. For SSA, we did not find similar population-based studies, but in a hospital-based study of individuals with psychosis, PLWH were more likely to be cognitively impaired [28].

Population-based studies of diabetes and hypertension in SSA have reported better outcomes for PLWH. In a previous study using HAALSI data, PLWH averaged lower SBP and lower prevalence of diabetes [18]. In a Ugandan study, HIV infection was associated with approximately 3.3 mmHg lower SBP and 30% lower odds of hypertension [29]. These associations may be due to lower BMI among PLWH, since BMI is a risk factor for both hypertension and diabetes [30].

Differential access to healthcare for PLWH compared to HIV negative comparators is also possible. In a previous study using data from HAALSI, PLWH were more likely to have had their blood pressure and blood sugar measured, more likely to have received counseling on exercise, more likely to be aware of their hypertension status and, as such, more likely to have been treated [18]. In HAALSI, a large proportion (69%) of PLWH are receiving ART. HIV care programs in SSA are often vertical programs that are more intensively managed, which may lead to better services than the general healthcare system serving individuals without HIV [31, 32]. It is unclear if these mechanisms might contribute to better cognitive outcomes for PLWH, and this may warrant future study.

In addition to these possibilities, selective survival among PLWH may explain apparent cognitive advantage, if more vulnerable PLWH died before cross-sectional sampling of the HAALSI baseline data occurred. A selected group of PLWH who are robust to the physical and cognitive consequences of HIV may then be sampled. This mechanism is consistent with our analyses assessing for interaction between age and HIV on the conventional measure of cognitive function where older PLWH had higher cognitive

scores than HIV-negative comparators. Future longitudinal studies are important to better understand this issue.

Other selection processes influencing initial infection risk, sampling, or data availability also may shape cognitive patterns in the HAALSI sample. For example, very old and very sick PLWH might not have been interviewed. Cognitive advantage however was not observed among PLWH on the OCS-Plus measure, raising doubts on this mechanism. Numerous unmeasured factors may also have influenced HIV infection and cognition since, despite adjustment for confounders, we cannot rule out the possibility of residual confounding in an observational study. In particular, literacy bias could give advantage to PLWH if literacy differences are not adequately controlled for by adjustment for education level.

Although the sample size in the OCS-Plus analysis was small leading to inconclusive results, findings using this measure were more consistent with our prior expectation of a cognitive disadvantage among PLWH. Future studies using this measure and other novel cognitive function assessment tools designed to be more appropriate in low-literacy settings are recommended [33].

Our results should not be interpreted as causal given the several competing alternative explanations. Regardless, even if not causal, our findings have important implications for policies aimed at providing care to aging cohorts of PLWH in SSA. If PLWH are systematically more likely to have cognitive impairment, policies to provide for HIV treatment and management would need to be designed to accommodate such impairments. If selective survival within PLWH means that we are only observing a small group of more robust survivors, then we do not know what the pattern of cognition would have been in the non-survivors. Increased access to ART, especially if treatment occurs early in the course of HIV-infection, as is likely to happen with the current policy of “test and treat”, may eliminate such selective survival allowing for better future exploration of the effects of both HIV and ART on cognition.

A cognitive advantage in PLWH on the other hand, if confirmed may mean that a growing number of older adults living with HIV may not necessarily cause an epidemic of HIV-associated dementia. A broader range of interventions and programs to provide for ongoing management of HIV infection in

older adults may then be needed. But even then, support to those with more severe cognitive impairment and/or their caregivers may be needed, since social programs to support elderly and cognitively impaired individuals are largely unavailable in SSA.

Our study provides unique data comparing HIV infected individuals to uninfected individuals with similar sociodemographic backgrounds in a setting of high HIV prevalence and where ART is now widely available through the public health sector. Objective measures on HIV status and ART use, as well as multiple cognitive function measures add to the strengths of our observations, but due to their cross-sectional nature, the data do not necessarily describe causal effects of HIV on cognition. We therefore recommend future longitudinal studies to further explore cognitive differences between HIV-positive and HIV-negative individuals in this setting and to further develop measurement tools that may be more appropriate for this and similar settings.

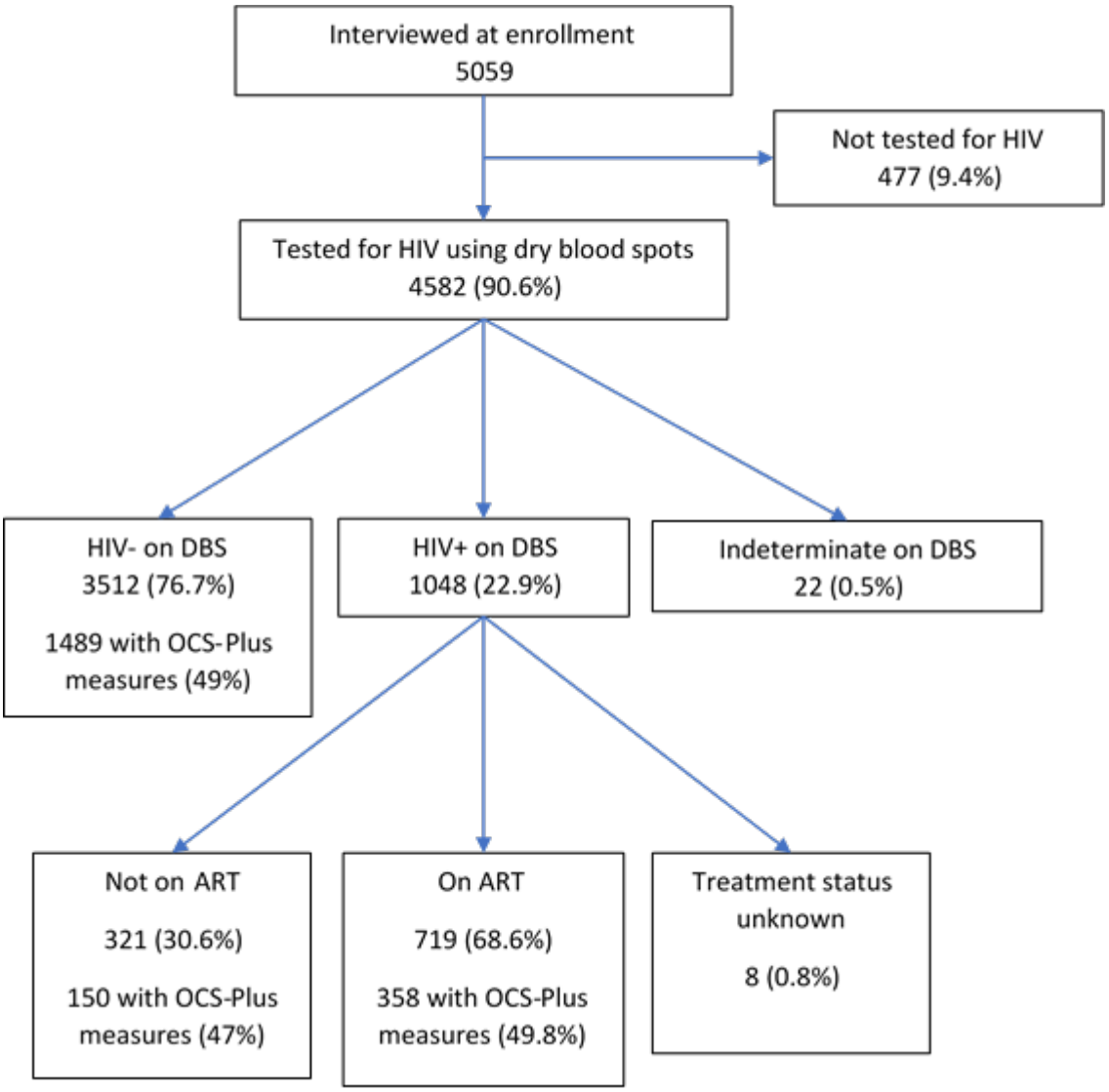


Figure 1.1. Selection of analytic sample from participants in "Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa" (HAALSI)

Fig. 2.1a. *HIV infection vs. cognitive performance*

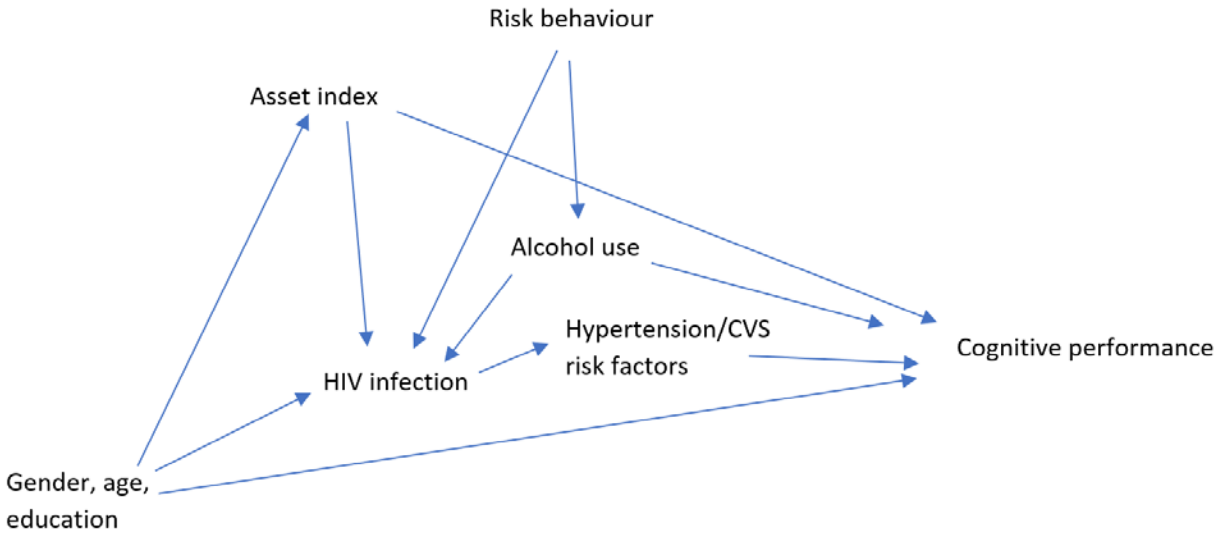


Fig. 2.1b. *ART vs. cognitive performance*

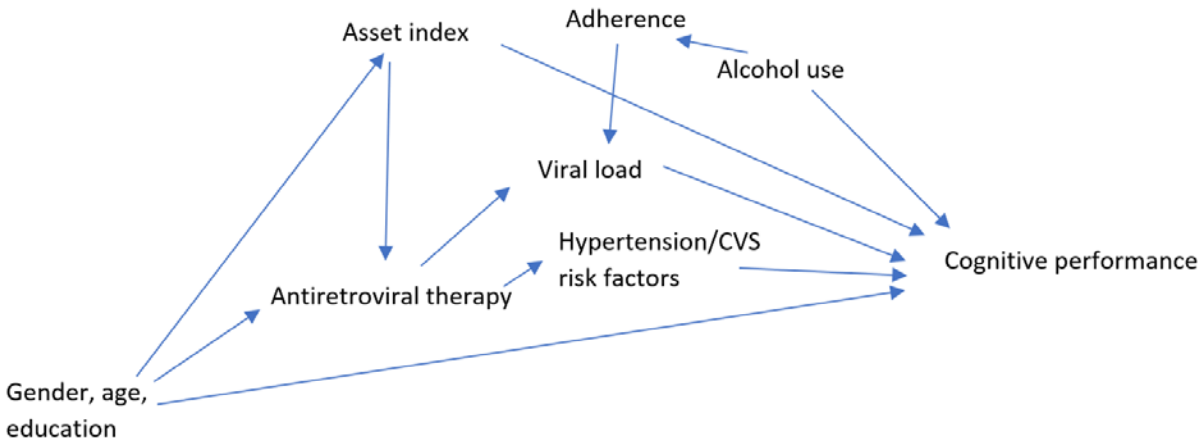


Figure 1.2. Directed acyclic graphs depicting possible relationships between HIV (2.1a) and ART (2.1b) and cognitive performance

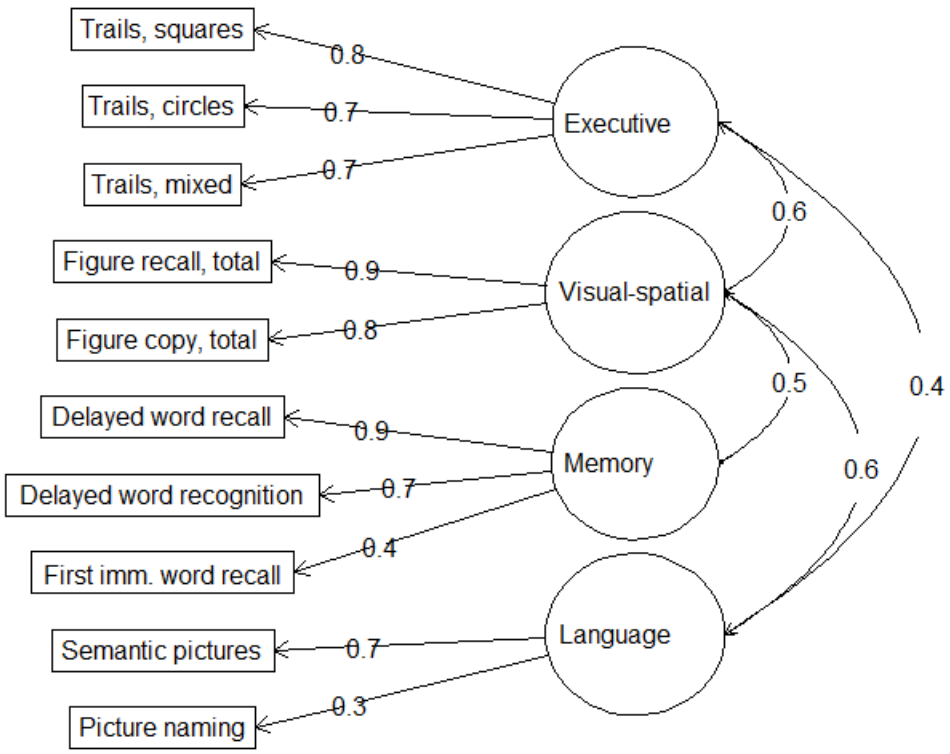


Figure 1.3 Factor loadings from a confirmatory factor analysis of 10 items from the OCS-Plus measure of cognitive function in "Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa" (HAALSI)

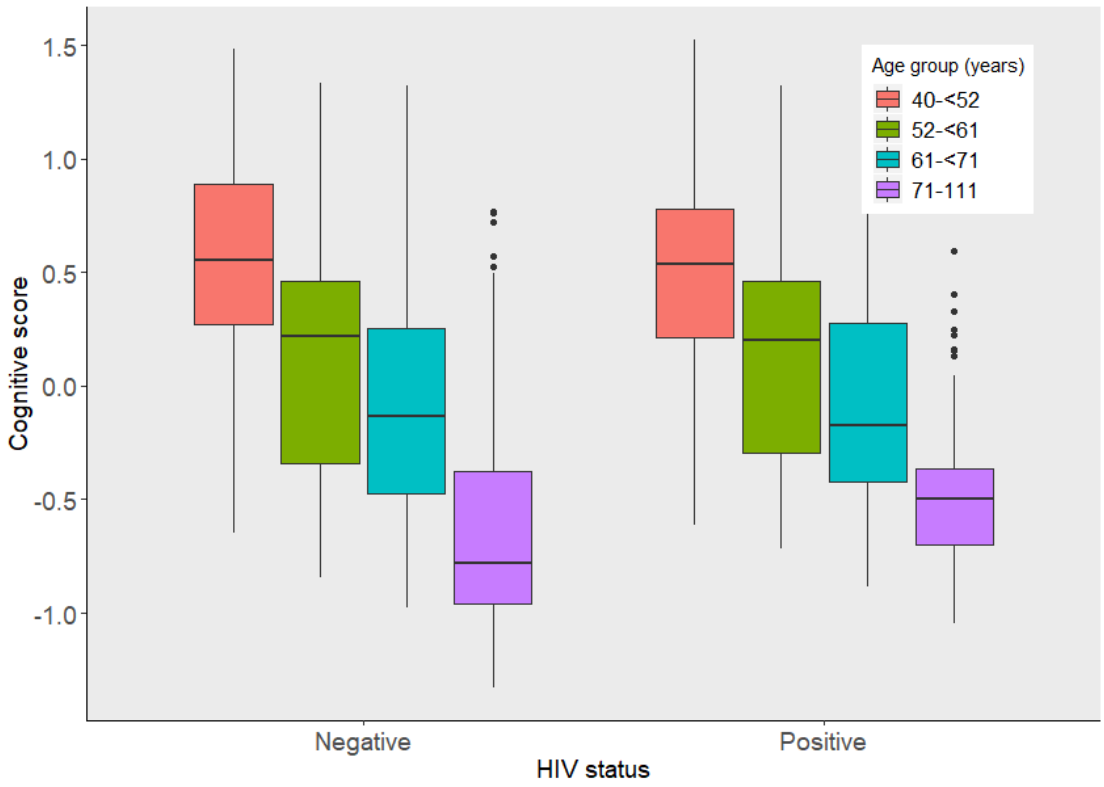


Figure 1.4. Age-HIV interaction in predicting cognitive score on the conventional measure by quartiles of age

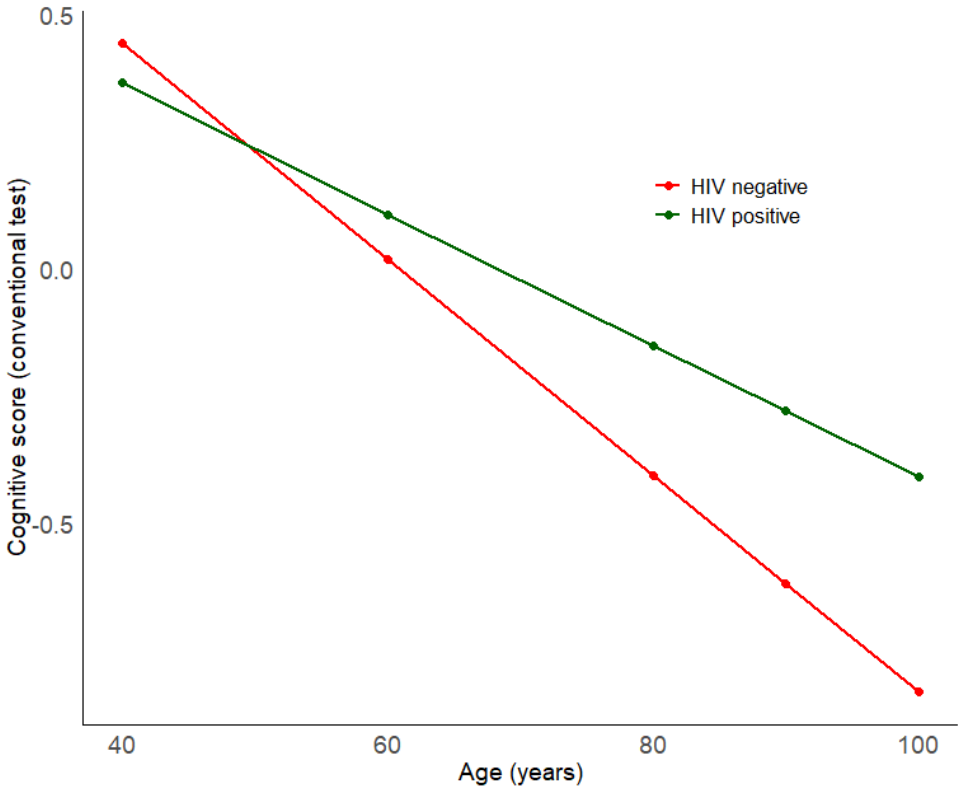


Figure 1.5. Age-HIV interaction in predicting cognitive score on the conventional measure with age as a continuous variable

Table 1.1. Characteristics of baseline participants (N = 4560) in Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI), Agincourt, South Africa, 2015

Characteristic	HIV-negative (N = 3512)	All HIV-positive (N = 1048)	ART users (N=719)	Non-ART users (N = 321)
Age, years	64 (13)*	55 (10)	56 (10)	55 (11)
Men (N, %)	1614 (46%)	483 (46%)	339 (47%)	140 (43%)
Country of birth, N (%)				
South Africa	2486 (71%)	683 (65%)	477 (66%)	202 (64%)
Mozambique/Other	1024 (29%)	363 (35%)	240 (33%)	119 (37%)
Father's occupation				
Manual labor	1950 (56%)	558 (56%)	414 (58%)	169 (53%)
Services	349 (9.9%)	104 (9.9%)	78 (11%)	26 (8.1%)
Self-employed or business	111 (3.2%	34 (3.2%	22 (3.1%)	12 (3.7%)
Professional	302 (8.6%)	106 (10%)	73 (10%)	33 (10%)
Other	387 (11%)	130 (12%)	83 (14%)	46 (14%)
Don't know or refused	412 (12%)	85 (8.1%)	48 (11%)	35 (11%)
Education (N, %)				
No formal education	1660 (47%)	429 (41%)	286 (40%)	141 (44%)
Some primary education	1225 (35%)	364 (35%)	263 (37%)	96 (30%)
Some secondary education	345 (9.8%)	162 (16%)	107 (15%)	54 (17%)
Secondary or more	272 (7.7%)	89 (8.5%)	60 (9.0%)	29 (8.3%)
Ever consumed alcohol	1564 (46%)	470 (45%)	339 (47%)	128 (40%)
Asset index score, mean (SD)	0.10 (2.4)	-0.31 (2.2)	-0.22 (2.2)	-0.48 (2.2)

Characteristic	HIV-negative (N = 3512)	All HIV-positive (N = 1048)	ART users (N=719)	Non-ART users (N = 321)
Systolic BP, mmHg	140 (23)	130 (22)	129 (22)	133 (22)
Diastolic BP, mmHg	83 (13)	81 (13)	80 (13)	83 (12)
Hemoglobin, mg/dl	12.7 (2.0)	12.1 (1.9)	12.1 (2)	12.2 (1.7)
Viral load, copies/ml	-	16191 (136351)	1499 (11668)	49034 (242627)

*Mean (SD)

Table 1.2. Cognitive outcomes on conventional and OCS-Plus cognitive batteries, according to HIV status, HAALSI, Agincourt, South Africa, 2015.

Measures	**HIV-negative (N=3512)**	**All HIV-positive (N=1048)**	**HIV-positive ART users (N=719)**	**HIV-positive ART non-users (N=321)**
Conventional measures				
Orientation (N giving correct response)				
Current date, N (%)	2382 (88%)	838 (80%)	579 (81%)	252 (79%)
Current month, N (%)	2749 (78%)	916 (87%)	633 (88%)	277 (86%)
Current year, N (%)	2506 (71%)	850 (81%)	583 (81%)	262 (82%)
Current president, N (%)	2794 (80%)	893 (85%)	619 (86%)	268 (84%)
Word recall (number of words)				
Immediate, median (IQR)	4 (3 to 5)	5 (3 to 6)	4 (3 to 6)	5 (3 to 6)
Delayed, median (IQR)	4 (2 to 5)	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)
Numeracy (N responding correctly)				
Forward count (1 to 20), N (%)	2636 (75%)	867 (83%)	605 (84%)	256 (80%)
Skip pattern, N (%)	1892 (54%)	655 (63%)	452 (63%)	198 (62%)
Cognitive score, mean (SD)	-0.06 (0.99)	0.19 (0.94)	0.20 (0.92)	0.18 (0.99)
OCS-Plus, correct responses, median (IQR)	**HIV-negative N = 1489**	**All HIV-positive N = 505**	**HIV-positive ART users N=358**	**HIV-positive ART non-users N=150**
Executive function				
Trails, circles	3 (1 to 6)	4 (2 to 7)	4 (2 to 7)	4 (1 to 6)

OCS-Plus, correct responses, median (IQR)	**HIV-negative N = 1489**	**All HIV-positive N = 505**	**HIV-positive ART users N=358**	**HIV-positive ART non-users N=150**
Trails, squares	3 (0 to 5)	4 (1 to 5)	3 (1 to 5)	4 (1 to 5)
Trails, mixed	3 (1 to 6)	4 (1 to 7)	4 (2 to 7)	4 (1 to 6)
Language				
Picture naming	3 (3 to 4)	3 (2 to 3)	3 (2 to 3)	3 (2 to 3)
Semantic pictures	3 (2 to 4)	3 (3 to 4)	4 (3 to 4)	3 (3 to 4)
Visual-spatial ability				
Figure copy	19 (17 to 20)	19 (16 to 20)	19 (16 to 20)	20 (17 to 21)
Figure recall	17 (12 to 19)	17 (12 to 19)	16 (12 to 19)	18 (14 to 20)
Memory				
First immediate word recall	3 (3 to 4)	4 (2 to 4)	4 (3 to 4)	3 (3 to 4)
Delayed word recall	3 (2 to 4)	3 (2 to 4)	3 (2 to 4)	3 (2 to 4)
Delayed word recognition	5 (4 to 5)	5 (4 to 5)	5 (4 to 5)	5 (4 to 5)

Table 1.3. Associations between HIV status, ART use, and the conventional cognitive battery z-score, HAALSI, Agincourt, South Africa, 2015.

	Model 1*	Model 2†
HIV status (N = 4480)		
HIV-Negative	Ref.	Ref.
HIV-Positive (β, 95% CI)	0.06 (0.01 to 0.12)	0.07 (0.01 to 0.12)
Treatment status among HIV-positive (N = 1020)		
ART non-user	Ref.	Ref.
ART user (β, 95% CI)	-0.01 (-0.12 to 0.09)	-0.05 (-0.20 to 0.10)

*Adjusted for age, sex, education, father's occupation, country of birth, asset index score, ever consumed alcohol

†Adjusted for above confounders plus systolic blood pressure, diastolic blood pressure, and in analyses of the effects of ART treatment status, viral load.

Table 1.4. Association of HIV status by ART use status with cognitive scores using a three-level categorical variable of HIV-positive ART users vs. HIV-positive ART non-users vs. HIV-negative participants with HIV-negative participants as reference.

	Model 1	**Model 2**
Conventional measure		
HIV-negative	Ref.	Ref.
HIV-positive ART user	0.06 (-0.001 to 0.13)	0.07 (0.002 to 0.13)
HIV-positive ART non-user	0.06 (-0.03 to 0.15)	0.07 (-0.03 to 0.16)
Summary OCS-plus measure		
HIV-negative	Ref	Ref
HIV-positive ART user	-0.04 (-0.10 to 0.03)	-0.03 (-0.09 to 0.04)
HIV-positive ART non-user	-0.07 (-0.17 to 0.03)	-0.07 (-0.17 to 0.03)

Table 1.5. Associations between HIV status, ART use, and domain-specific cognitive function as measured on the OCS-Plus instrument, HAALSI, Agincourt, South Africa, 2015

			Domain specific effect[†]							
	Main effect[*]		Memory		Language		Visual-spatial		Executive	
	Model 1[‡]	*Model 2*	*Model 1*	*Model 2*	*Model 1*	*Model 2*	*Model 1*	*Model 2*	*Model 1*	*Model 2*
HIV status										
Negative	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Positive	-0.03 (-0.09 to 0.03)	-0.03 (-0.08 to 0.03)	-0.01 (-0.09 to 0.06)	-0.01 (-0.08 to 0.07)	-0.04 (-0.12 to 0.04)	-0.04 (-0.12 to 0.04)	-0.02 (-0.10 to 0.07)	-0.02 (-0.10 to 0.07)	-0.02 (-0.10 to 0.07)	-0.02 (-0.10 to 0.07)
ART status										
Non-user	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
ART user	0.03 (-0.08 to 0.13)	0.01 (-0.14 to 0.16)	0.10 (-0.04 to 0.24)	0.08 (-0.10 to 0.26)	-0.07 (-0.22 to 0.09)	-0.07 (-0.22 to 0.09)	-0.16 (-0.32 to -0.01)	-0.15 (-0.32 to -0.01)	-0.05 (-0.20 to 0.11)	-0.05 (-0.20 to 0.11)

[*]Without interaction term between measure and predictor
[†]With interaction between measure and predictor
[‡]Model 1 is adjusted for age, sex, education, country of origin, father's occupation, asset index score, and alcohol ever use. Model 2 is further adjusted for blood pressure, and in those with HIV for the treatment analysis, viral load.

Table 1.6. Association of HIV status and treatment status with a summary OCS-Plus measure of cognition adjusted for confounders

	Model 1*	**Model 2†**
HIV status (N = 4480)		
HIV-Negative	Ref.	Ref.
HIV-Positive (β, 95% CI)	-0.03 (-0.10 to 0.03)	-0.03 (-0.09 to 0.04)
Treatment status among HIV-positive (N = 1020)		
ART non-user	Ref.	Ref.
ART user (β, 95% CI)	0.03 (-0.09 to 0.15)	0.01 (-0.17 to 0.19)

Table 1.7. Interaction between age and HIV in their association with cognition adjusted for confounders

	Conventional measure	**OCS-Plus measure**
HIV-Negative	Ref.	Ref.
HIV-Positive (β, 95% CI)	0.11 (0.05 to 0.18)	-0.078 (-0.14 to 0.001)
Centered Age (β, 95% CI)	-0.021 (-0.024 to -0.019)	-0.014 (-0.017 to -0.010)
HIV-Positive: Age (β, 95% CI)	0.01 (0.004 to 0.014)	-0.01 (-0.01 to 0.001)

Chapter 2 : HIV status and antiretroviral therapy as predictors of disability among older South Africans: Do the associations depend on body mass index?

Background

People living with HIV (PLWH) may experience premature age-related disability [1-3]. Also, increased access to antiretroviral therapy (ART) has substantially increased the survival of PLWH into older age [4]. Consequently, age-related disability is an important concern for PLWH, their caregivers, and health systems in settings with high HIV prevalence [5, 6].

In sub-Saharan Africa (SSA), the region with the world's highest HIV prevalence, few population-based studies have described age-related disability in PLWH. In the general population, HIV infection is often associated with poor health [7] and may through this or other pathways increase risk of disability. In those with HIV, ART use improves health [8-10] and could thus reduce risk of age-related disability. There is very little empirical confirmation of these expected patterns, however, because few studies have been able to compare PLWH to HIV negative comparators and, PLWH, ART users to non-users. Overall, the extent to which HIV increases risk of disability in older adults and whether ART use mitigates this effect remains unclear [11-15].

ART use also often causes weight gain [16] and could counter-intuitively increase risk of age-related disability in PLWH through obesity. Literature from high-income settings suggests that high BMI (compared to normal or low BMI) increases risk of disability [17]. This is also a concern in SSA, given the rapidly unfolding obesity epidemic [18]. However, HIV-infected patients in SSA often have high rates of malnutrition, which is strongly associated with negative health outcomes [19, 20]. A South African study, which assessed BMI among ART-treated PLWH (with at least 6 months of ART use) reported no association with disability, but neither the distribution of BMI nor its form (e.g., linear vs. flexible) in the analyses were reported [21]. However, a study of population-level trends in BMI following the introduction of ART found an overall decrease in BMI and suggested that increased survival of largely underweight PLWH may have masked any ART-related increases in BMI [22].

Without empirical data on the role of HIV in age-related disability, HIV treatment programs in SSA cannot adequately respond to the needs of an increasingly older population of PLWH. Responses such as addition of rehabilitative programs to HIV care [23], making HIV treatment clinics more accessible to people with disability [8, 24, 25], and possibly novel interventions to prevent or delay age-related disability, will become more urgent as the burden of age-related disability increases. For example, if BMI either modifies or mediates effects of HIV and/or ART on disability, care may be improved by monitoring and potentially intervening on factors influencing weight change. Alternatively, if BMI merely modifies effects of HIV and/or ART on disability, groups at high risk of disability might be simply targeted with interventions to reduce disability even if those interventions do not weight change.

The "Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa" (HAALSI), a population-based cohort of older individuals in South Africa, is collecting data that could facilitate population-based analyses on HIV and age-related disability [26]. Two prior studies from HAALSI have reported on HIV infection as a correlate of limitations in activities of daily living (ADL), but their results differed [13, 15]. The studies were not specifically designed to address the effects of HIV on disability but suggest sensitivity to analytic decisions, especially how confounders for multivariable regression models are selected. Neither study addressed the role of ART use or BMI.

In the cross-sectional data currently available in HAALSI, if effects of HIV or ART depend on BMI, it is impossible to distinguish between BMI at cohort entry modifying HIV or ART effects on disability, versus BMI being a mechanism that links an HIV diagnosis or ART initiation to subsequent disability. However, either result is important for guiding care. For example, groups at increased risk of disability may be identified. Results may indicate whether interventions to directly address underweight or obesity should be prioritized. Finally, the results may guide hypotheses for future longitudinal studies. We therefore aimed to evaluate the association of HIV and ART with ADL disability in the HAALSI sample of older African individuals, and to assess whether these associations depend on BMI, hypothesizing that in this setting both low and high BMIs might increase risk of disability.

Methods

Study setting and ethics statement

The data were from HAALSI, a population-based cohort study enrolling men and women aged at least 40 years and living in Agincourt, Mpumalanga, South Africa. The characteristics of this cohort have been previously reported [26]. Sampling was done from the 2013 census round under the MRC/Wits-Agincourt Health and socio-Demographic Surveillance System (HDSS), which is part of the International Network for the Demographic Evaluation of Populations and their Health (INDEPTH).

Ethics statement

Participants provided written informed consent, and ethics committees at the University of the Witwatersrand, South Africa, the Harvard T.H. Chan School of Public Health, and the Mpumalanga Provincial Research and Ethics Office, approved HAALSI. The ethics committee at UCSF also reviewed and approved our proposal to access and analyze HAALSI data.

Design

We performed a cross-sectional analysis of HAALSI baseline data restricting the analysis to participants who had biological HIV tests from dried blood spots (N = 4552 (90%) of 5059).

Measures

HIV and ART use were the primary predictors. Biological measurements were used. Dried blood spots were collected for HIV status, plasma HIV RNA levels (viral load), and drug measurements (emtricitabine and lamivudine), as previously described [28]. PLWH testing positive for either emtricitabine or lamivudine, two drugs that are used interchangeably in initial ART regimens were considered as ART users. All participants with HIV were tested for HIV viral load. Individuals testing negative for antiretroviral drugs but who were virally suppressed were considered ART users [27].

As the effects of ART may depend on whether viral suppression is achieved, in addition to comparing ART users to non-users, we created an additional categorical predictor taking viral suppression into

consideration. This variable grouped participants with HIV into: those that were virally suppressed, all of whom were considered treated (viral load <100 copies/ml) (N = 537), vs. those that were treated but unsuppressed (positive for ART but with detectable viral load at the ≥100 copies/ml cut-off) (N = 183), vs. those that were untreated (negative for ART and with viral load ≥100 copies/ml) (N = 321) [28].

BMI was calculated from measured weight and height and considered as a potential mediator and/or modifier of the effects of HIV infection and of ART treatment, acknowledging that the temporal order is uncertain in a cross-sectional data set. We categorized BMI values as per previous studies [19, 20] into underweight (<18.5kg/m^2), normal BMI (18.5 to <25), overweight (25 to <30) and obese (≥30).

Limitation in any of 5 basic ADLs was assessed as the primary outcome. Participants were asked about their ability to perform the following activities: walking across the room, dressing, bathing, using the toilet and getting out of bed. Participants were classified as being disabled on an activity if they were unable to perform the activity; had difficulty performing the activity; used equipment when performing the activity; or received help from another person to perform the activity. The final outcome measure was a binary variable describing presence of at least one disability versus none [13].

We represented our assumptions guiding covariate selection for the analyses using a DAG (**Figure 2.1**). Increasingly, most PLWH will receive ART regardless of their characteristics in the setting of "test and treat", the current approach to HIV treatment [29]. However, treatment is not yet universal in South Africa and sociodemographic factors may influence the timing of ART initiation. Covariates considered as potential confounders in all regression models were age and sex [30]. A second group of covariates obtained from study interviews was added to a more comprehensively adjusted regression model (model 2). These covariates included father's occupation (professional, self-employed, business, or services, vs. manual labor, other or don't know) to capture influences of cross-generational social status, and country of origin (South Africa vs. Mozambique or other), since the study area borders Mozambique and migrant residents may have been differentially exposed to structural health risk factors [31]. We also adjusted in these regression models for the participant's own education (no formal education or some primary

education vs. some secondary education, or full secondary education or more) to account for possible education-related differences, and alcohol consumption ever in the participant's life to account for possible differences in risk behaviors.

Statistical analysis

Based on logistic regression models, we estimated the marginal mean prevalence (Stata 15, College Station, Texas) of ADL disability comparing participants with HIV to those without HIV, and, among participants with HIV, ART users to non-users. In additional analyses considering the viral load, we compared suppressed ART users vs. unsuppressed ART users vs. non-users. BMI was conceptualized as either a potential mediator or effect modifier, but we could not distinguish between these alternatives.

For each primary predictor (HIV or ART use), we fit a regression model adjusting for age and sex (model 1), and a regression model further adjusting for education, father's occupation, country of origin, and alcohol ever use (model 2).

We estimated models with and without an interaction term between BMI and the primary predictor. Estimates from the interaction models are reported as marginal predictions of the prevalence of ADL disability in strata of the primary predictors and BMI categories with associated prevalence differences (estimated with Stata 15). Covariates were centered at their mean values. HIV negative participants with normal BMI and ART users with normal BMI were the reference categories for the HIV and ART predictors respectively. When comparing suppressed ART users vs. unsuppressed ART users vs. ART non-users among PLWH, suppressed ART users were the reference category. In additional analyses, we assessed both age and BMI modeled flexibly as restricted cubic splines in logistic regression models (estimated with R Statistical Software) predicting probability of an ADL disability in participants with HIV and those without HIV. Observations from these analyses are presented graphically.

Results

Sample characteristics

Among 4552 participants included in the analyses, 1040 (23%) were PLWH. Exclusions from the main sample (N = 5059) were: not tested for HIV (N = 477), indeterminate HIV test results (N = 22), and ART use not established (N = 8). Among PLWH, 719 (69%) were ART users. PLWH were younger (mean age 55 (SD = 10) vs 64 (SD = 13)), more likely to be underweight (7.4% vs. 4.6% in those without HIV) and less likely to be obese (21% vs 30%) than those without HIV. Among PLWH, ART users were slightly more likely to be underweight than non-users (7.5% vs. 6.5%, respectively). Among all participants, the proportion with an ADL disability was 11.9% (8.6% in PLWH vs. 12.9% in those without HIV) (**Table 2.1**).

HIV status, BMI and ADL disability

Adjusting for confounders underweight participants had higher prevalence of ADL disability than normal BMI participants (**Tables 2.2 and 2.3**). For example, underweight PLWH had 13.3 percentage points (95% CI 3.8 to 22.9) higher prevalence of an ADL disability than PLWH with normal BMI. Participants with obesity had 2.9 percentage points (95% CI: -2.3 to 8.1) higher prevalence of an ADL disability than those with normal BMI, this result not reaching statistical significance (**Table 2.3**). Predicted probability of an ADL disability was elevated for HIV-negative participants at low BMI (**Figure 2.2**).

ART use, BMI and ADL disability among PLWH

Among PLWH, adjusting for confounders, underweight ART users also had higher prevalence of an ADL disability (**Tables 2.4 and 2.5**). For example, underweight ART users had 13.7 percentage points (95% CI 2.8 to 24.4) higher prevalence of an ADL disability than normal weight ART users. Overweight ART non-users had 5.2 percentage points (95% CI: -2.8 to 13.1) higher prevalence of an ADL disability, this result not reaching statistical significance. Obese ART users had 1.2 percentage points (95% CI -4.3 to 6.9) higher prevalence of an ADL disability than those with normal BMI, this result not statistically significant (**Table 2.5**).

The effects of ART use somewhat varied according to BMI and viral load categories although sample sizes for these additional analyses were small. For example, adjusting for age and sex, underweight suppressed ART users had 16.0 percent points (95% CI 2.8 to 30.1) higher prevalence of an ADL disability than normal BMI suppressed ART users. Overweight ART non-users had 6.0 percentage points (95% CI -2.2 to 14.2) higher prevalence of an ADL disability than normal BMI suppressed ART users, this result not reaching statistical significance (**Supplementary table 1.2**). For all PLWH (treated suppressed, treated unsuppressed, and untreated PLWH), predicted probability of an ADL limitation was generally higher at low BMIs compared to normal or high BMIs (**Figure 2.3**).

The independent associations of HIV and ART use with ADL disability

In covariate-adjusted regression models without the interaction of HIV and ART with BMI, prevalence of an ADL disability was similar between PLWH and participants without HIV (adjusted prevalence difference (APD) 0.8 percentage points, 95% CI -1.8 to 3.4). Among PLWH, ART users had similar prevalence of ADL disability as non-users (APD 0.5, 95% CI, -3.1 to 4.2). Treated suppressed PLWH were as likely to have an ADL disability as treated unsuppressed, or untreated participants (APD 2.2, 95% CI -2.7 to 7.2 comparing unsuppressed ART users vs. suppressed ART users, and APD 0.03, 95% CI -3.8 to 3.8 comparing ART non users to suppressed ART users) (**Supplementary table 2.2**).

The independent association of age and BMI with ADL disability

Prevalence of ADL disability increased with age for all participants (APD per SD increase in age = 4.0, 95% CI 3.2 to 4.8) (**Supplementary table 2.3**). However, at no age did the predicted prevalence of disability diverge substantially for people with vs without HIV (**Figure 2.4**). Adjusting for HIV status and other covariates, underweight participants had 4.7 percent points (95% CI 0.5-8.9) higher prevalence of an ADL disability than normal BMI participants. Obese participants had about 1.6 percentage points (95% CI: -0.7 to 3.9) higher prevalence of an ADL disability than those with normal BMI, this result not reaching statistical significance (**Supplementary table 2.3**).

Discussion

In this population-based sample of older adults in rural South Africa, participants with HIV overall had similar prevalence of an ADL disability as those without HIV. Among the participants with HIV, ART users also had similar prevalence of ADL disability as non-users. However, regardless of HIV status, ART use or viral suppression, underweight participants had increased prevalence of an ADL disability.

The association of HIV and ART with disability thus depended on BMI values, but given the cross-sectional nature of these data, we cannot distinguish between BMI acting as a mediator versus BMI acting as a modifier of the effects of HIV and ART on ADL disability. In a mediating role, underweight status would act as a mechanism linking HIV and/or ART to subsequent disability. Interventions to increase weight such as nutritional supplementation might then be hypothesized as able to reduce risk of disability. This is a possibility since HIV infection is strongly associated with malnutrition in SSA [19]. Malnutrition in HIV infection is also linked to muscle-weakness [32], a potential cause of ADL disability.

Alternatively, if BMI merely modifies the effect of HIV or ART on disability, an important question is whether there are groups of HIV-positive or HIV-negative individuals for whom disability occurs only in presence of certain BMI values. Population-level interventions against disability (regardless of whether such intervention affect weight) might then target such groups. Observing such groups may also shed some light on potential mechanisms via which HIV and ART influence disability.

Our results indicate that disability occurs more frequently in underweight groups irrespective of HIV status, ART use, or viral load. Targeting underweight individuals with some interventions may thus be reasonable. The content of such interventions should be addressed by future studies. There are very few prior studies in the region that have investigated BMI or other measures of nutritional status as predictors of age-related disability. However, in a cross-sectional study of PLWH in South Africa, low albumin, a nutrition-status biomarker was associated with functional limitations [33]. As we are unable to establish a causal role for BMI, we cannot say that interventions changing BMI would reduce risk of disability.

Moreover, factors causing low BMI may be nutritional but could also be due to underlying diseases such as tuberculosis, which would need to be identified and treated.

Prior data suggest that ART may protect against ADL disability. In a previous study among PLWH conducted in South Africa, rural participants on ART were 17% less likely to require assistance with instrumental activities of daily living (IADL) than counterparts not receiving ART at any clinic visit adjusting for multiple covariates (age, gender, education, marital status, income, healthcare utilization and the CD4+ T cell count). Urban-living ART users were 41% less likely to require assistance than their counterparts not using ART. ART users also had longer time to first IADL assistance in a Kaplan Meier analysis [9]. ART may protect against ADL disability since it generally improves the health of PLWH [10].

Despite these observations in prior studies, we did not see higher prevalence of ADL disability among ART non-users overall. ART non-users in our data were probably healthier than ART users; under earlier HIV care guidelines healthier individuals may have been deemed as "not yet eligible for ART". Selection can also occur within ART non-users, whereby any unhealthy individuals in the sub-group may have died prior to the HAALSI baseline sampling. This pattern tends to bias observations conservatively, and may have led to the observation of no difference by ART use status. The strong association of underweight with ADL disability and high rates of underweight among ART users could also mask benefits from ART.

We did not find evidence for increased risk of disability from obesity or overweight, which was surprising, since studies from high-income countries suggest that obesity is a risk factor for age-related disability. In the systematic review by Jiang et al (2018), obesity and overweight were associated with disability [17]. Underweight was also associated with disability in some of the studies [34, 35]. In our data, we also did not find differences overall by viral suppression status. As detectable viral load has been previously associated with ADL disability [6], this association should be further investigated in future longitudinal studies.

Our observations are limited by the cross-sectional nature of the data, hence inability to establish a temporal structure among the variables. However, a strengths of our study is biological HIV and ART measurements resulting in low risk of measurement error as a possible explanation for the observations. Despite their cross-sectional nature, our data add to the few population-based analyses available in SSA on the role of HIV in age-related disability and highlight the importance of underweight status in this population.

Our findings suggest the need for interventions to reduce age-related disability for all sub-groups in this population. However, underweight participants appear to be at an increased risk compared to everyone else and PLWH are more likely to be underweight. This observation suggests that targeting underweight PLWH for interventions to reduce disability may be a reasonable choice. Despite a relatively high prevalence of obesity in older South Africans, we did not find evidence for increases in disability from this risk factor. We recommend future longitudinal studies to further investigate BMI and ART effects, especially in the setting of early treatment for PLWH.

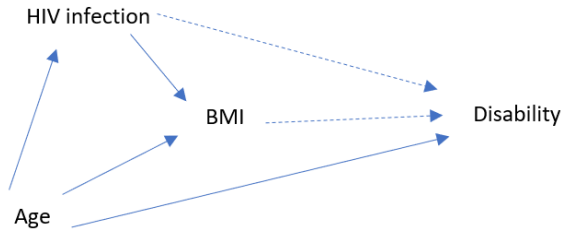
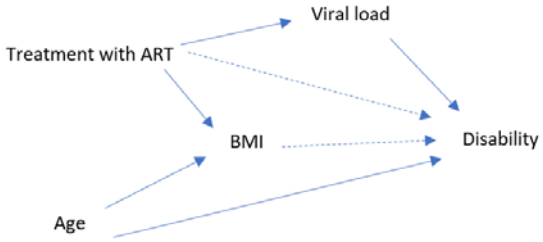
Figure 2.1a. HIV versus disability	*Figure 2.1b. ART versus disability*
	

Figure 2.1. Directed acyclic graphs for possible relationships between HIV infection and treatment with antiretroviral therapy (ART) and disability

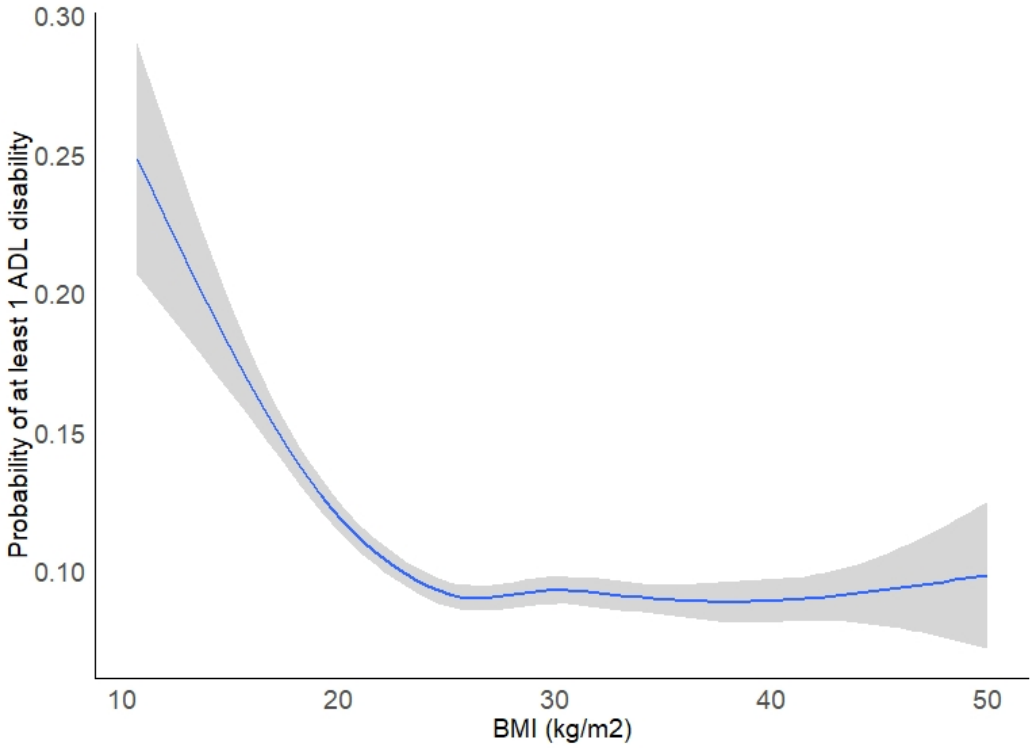


Figure 2.2. Smoothed relationships between BMI and predicted probability of an ADL disability among HIV-negative individuals in the HAALSI baseline sample (N = 3512). BMI was modelled as a 4-knots restricted cubic spline in logistic regression models predicting the probability of at least one ADL disability. Models were adjusted for age and sex.

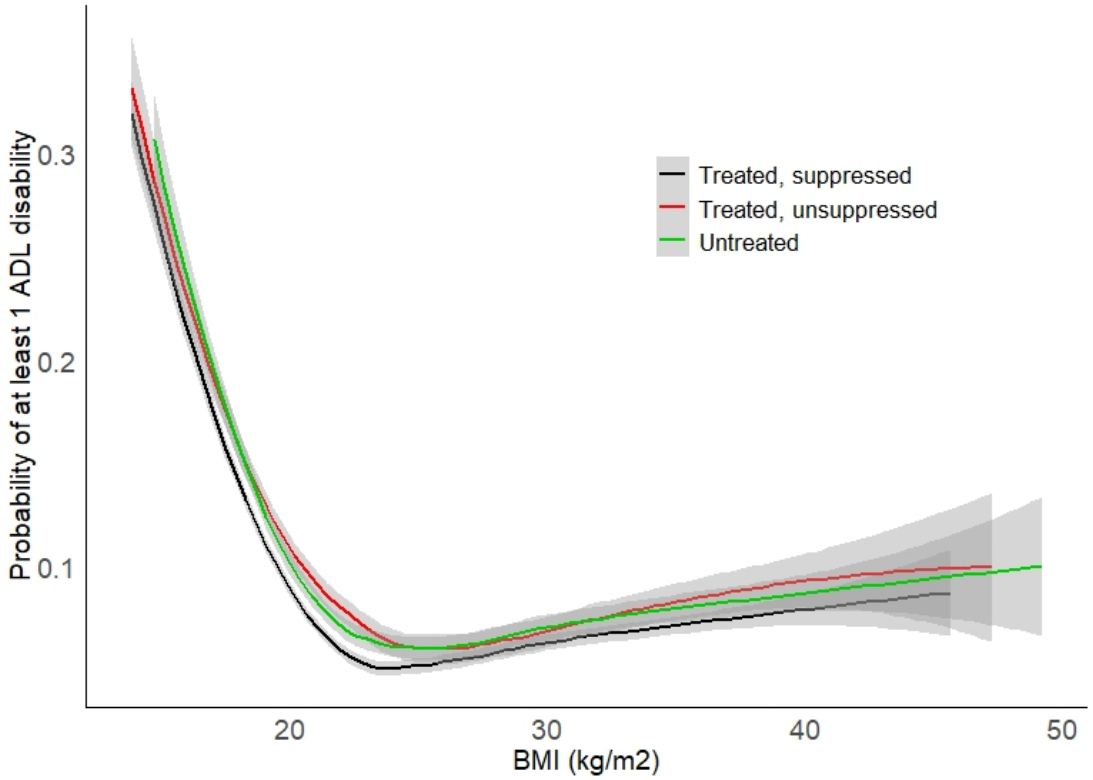


Figure 2.3. Smoothed relationships between BMI and predicted probability of an ADL disability by treatment and viral load status among participants with HIV (N = 1040). BMI was modelled as a 4-knots restricted cubic spline in logistic regression models predicting the probability of at least one ADL disability. Models were adjusted for age and sex.

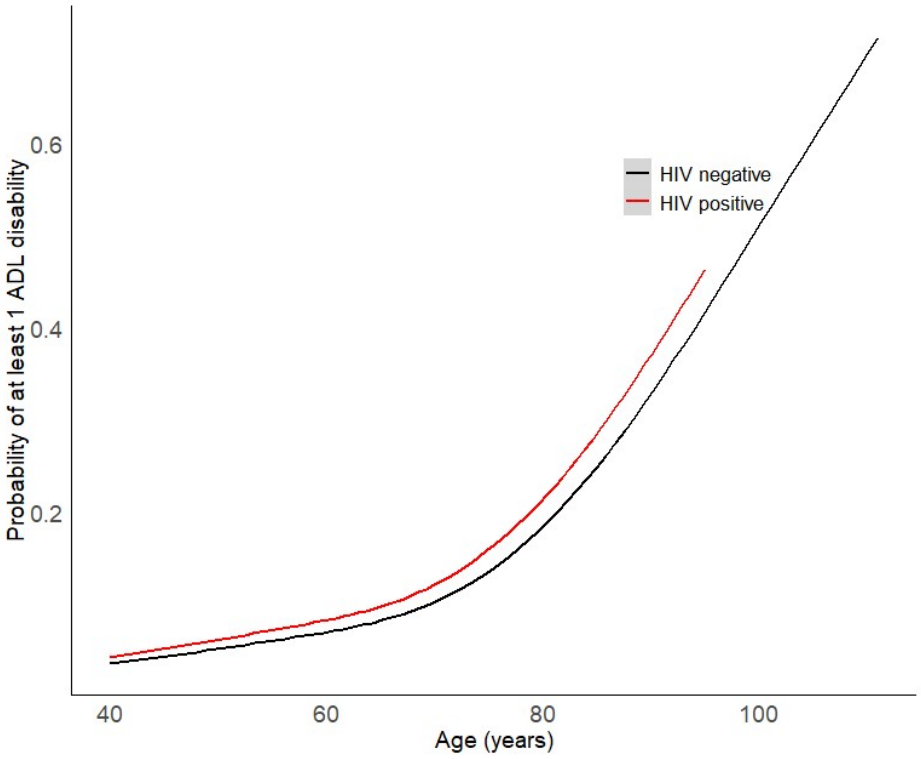


Figure 2.4. Smoothed relationship between age and predicted probability of an ADL disability by HIV status among HAALSI participants at baseline (N = 4452). Age was modelled as a 4-knots restricted cubic spline in logistic regression models to predict the probability of at least one ADL disability.

Table 2.1. The baseline characteristics of 4452 older South African adults at entry into the "Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa" (HAALSI). Interviews and measurements occurred from November 2014 to November 2015.

Variable*	All HIV positive (N = 1040)	HIV positive - Treated (N = 719)	HIV positive - Untreated (N = 321)	HIV negative (N = 3512)
Age, mean (SD)	55 (10)	56 (10)	55 (11)	64 (13)
Sex, female	561 (54%)	339 (47%)	140 (44%)	1898 (54%)
Log-10 viral load, mean (SD)	1.8 (1.8)	0.87 (1.3)	3.7 (0.98)	-
Viral load category				
Virally suppressed†	536 (52%)	536 (75%)	-	-
Unsuppressed	183 (18%)	183 (25%)	-	-
ART non-user	321 (30%)	-	321 (100%)	-
Education				
No formal education	427 (42%)	286 (40%)	141 (44%)	1660 (47%)
Some primary	359 (35%)	263 (37%)	96 (30%)	1225 (35%)
Some secondary	161 (15%)	107 (15%)	54 (17%)	345 (9.8%)
Secondary or more	89 (8.6%)	609 (8.0%)	29 (9.0%)	272 (7.7%)
Country of origin				
South Africa	679 (65%)	477 (66%)	202 (63%)	2486 (71%)
Other	359 (35%)	240 (33%)	119 (37%)	1024 (29%)
BMI (in kg/m^2)				
<18.5	75 (7.4%)	54 (7.5%)	21 (6.5%)	160 (4.6%)
18.5-<25	449 (43%)	312 (43%)	137 (43%)	1133 (32%)
25 -<30	259 (25%)	184 (26%)	75 (23%)	971 (28%)

Variable	All HIV positive (N = 1040)	HIV positive - Treated (N = 719)	HIV positive - Untreated (N = 321)	HIV negative (N = 3512)
≥30	223 (21%)	145 (20%)	78 (24%)	1064 (30%)
Missing	34 (3.3%)	24 (3.3%)	10 (3.1%)	184 (5.2%)
Fathers occupation				
Don't know	83 (8.0%)	48 (6.7%)	35 (11%)	412 (12%)
Manual labor	583 (56%)	414 (58%)	169 (53%)	1950 (55%)
Other	129 (12%)	83 (12%)	46 (14%)	387 (11%)
Professional	106 (10%)	73 (11%)	33 (10%)	302 (8.6%)
Self-employed or business	34 (3.3%)	22 (3.1%)	12 (8.1%)	111 (3.2%)
Services	104 (10%)	78 (11%)	26 (8.1%)	349 (9.9%)
Alcohol ever	467 (45%)	339 (53%)	193 (60%)	1564 (45%)
Basic ADL limitation, N (%)				
Walk across room	76 (7.3%)	56 (7.8%)	20 (6.2%)	406 (12%)
Dressing	27 (2.6%)	22 (3.1%)	5 (1.6%)	133 (3.8%)
Bathing	31 (3.0%)	25 (3.5%)	6 (1.9%)	152 (4.3%)
Getting out of bed	35 (3.4%)	26 (3.6%)	9 (2.8%)	209 (6.0%)
Using toilet	42 (4.0%)	31 (4.3%)	11 (3.4%)	255 (7.3%)
Any limitation	89 (8.6%)	63 (8.8%)	26 (8.1%)	453 (12.9%)

*N (%) unless otherwise stated; †viral load <100 copies/ml

Table 2.2. Prevalence differences and 95% confidence intervals for one or more limitations in 5 basic activities of daily living, by BMI category and HIV status (Model 1). Estimates adjusted for age and sex (model 1). Analysis among HAALSI baseline sample (N = 4452).

	HIV Negative		HIV positive	
BMI	**Prevalence of 1+ADL disability**	**Prevalence difference**	**Prevalence of 1+ADL disability**	**Prevalence difference**
Underweight	11.6 (7.2 to 16.1)	2.7 (-2.0 to 7.4)	23.7 (13.8 to 33.7)	14.8 (4.8 to 24.9)
Normal	8.9 (7.4 to 10.5)	Ref.	9.3 (6.3 to 12.4)	0.4 (-3.0 to 3.8)
Overweight	8.8 (7.1 to 10.5)	0.1 (-2.4 to 2.2)	9.6 (5.4 to 13.7)	0.6 (-3.8 to 5.1)
Obese	9.6 (7.8 to 11.4)	0.7 (-1.7 to 3.1)	11.3 (6.5 to 16.1)	2.4 (-2.8 to 7.5)

Table 2.3. Prevalence differences and 95% confidence intervals for one or more limitations in 5 basic activities of daily living, by BMI category and HIV status (Model 2). Estimates adjusted for age, sex, education, country of origin, father's occupation, and alcohol ever use (model 2). Analysis among HAALSI baseline sample (N = 4452).

	HIV Negative		HIV positive	
BMI	**Prevalence of 1+ADL disability**	**Prevalence difference**	**Prevalence of 1+ADL disability**	**Prevalence difference**
Underweight	10.8 (6.6 to 14.9)	2.0 (-2.3 to 6.5)	22.0 (12.6 to 31.3)	13.3 (3.8 to 22.8)
Normal	8.7 (7.2 to 10.2)	Ref.	9.0 (6.0 to 11.9)	0.3 (-3.0 to 3.6)
Overweight	8.6 (6.9 to 10.3)	-0.1 (-2.3 to 2.2)	9.5 (5.4 to 13.6)	0.8 (-3.6 to 5.3)
Obese	10.0 (8.1 to 11.9)	1.3 (-1.1 to 3.8)	11.5 (6.6 to 16.4)	2.9 (-2.3 to 8.1)

Table 2.4. Adjusted prevalence differences and 95% confidence intervals for one or more limitations in 5 basic activities of daily living (1+ADL) by BMI category and ART use status among people living with HIV (Model 1). Estimates adjusted for age and sex (model 1). Analysis among HAALSI baseline sample (N = 1040).

	ART non-user		**ART user**	
BMI	**Prevalence of 1+ADL disability**	**Prevalence difference**	**Prevalence of 1+ADL disability**	**Prevalence difference**
Underweight	9.2 (0 to 21.4)	2.1 (-10.4 to 14.5)	21.7 (10.8 to 32.7)	14.6 (3.4 to 25.9)
Normal	5.8 (1.9 to 9.7)	-1.3 (-6.2 to 3.5)	7.1 (4.3 to 10.0)	Ref.
Overweight	12.4 (4.9 to 20.0)	5.3 (-2.8 to 13.4)	4.4 (1.4 to 7.4)	-2.7 (-6.9 to 1.4)
Obese	8.3 (1.9 to 14.6)	1.1 (-5.9 to 8.2)	7.7 (3.3 to 12.1)	0.6 (-4.7 to 5.9)

Table 2.5. Adjusted prevalence differences and 95% confidence intervals for one or more limitations in 5 basic activities of daily living (1+ADL) by BMI category and ART use status among people living with HIV (Model 2). Estimates adjusted for age, sex, education, father's occupation, country of origin, and alcohol ever use (model 2), HAALSI baseline sample (N = 1040).

	ART non-user		**ART user**	
BMI	**Prevalence of 1+ADL disability**	**Prevalence difference**	**Prevalence of 1+ADL disability**	**Prevalence difference**
Underweight	8.7 (0 to 20.2)	1.7 (-10.2 to 13.5)	20.7 (10.1 to 31.3)	13.7 (2.8 to 24.4)
Normal	5.6 (1.8 to 9.4)	-1.4 (-6.1 to 3.3)	7.0 (4.2 to 9.8)	Ref.
Overweight	12.9 (5.1 to 20.6)	5.8 (-2.5 to 14.1)	4.4 (1.4 to 7.3)	-2.7 (-6.8 to 1.4)
Obese	8.9 (2.1 to 15.7)	1.9 (-5.6 to 9.3)	8.4 (3.6 to 13.1)	1.2 (-4.3 to 6.9)

Supplementary table 2.1. Prevalence differences for at least one ADL disability by ART use and viral load group and BMI category adjusted for age and sex. Analysis among HAALSI participants at baseline (n=1040).

	1+ADL disability, prevalence difference		
BMI	**Suppressed ART user**	**Unsuppressed ART user**	**ART non-user**
Underweight	16.5 (2.8 to 30.1)	12.5 (-6.8 to 31.8)	2.8 (-9.8 to 15.3)
Normal	Ref.	2.4 (-4.3 to 9.1)	0.1 (-5.7 to 4.4)
Overweight	-3.0 (-7.3 to 1.4)	1.0 (-7.7 to 9.7)	6.0 (-2.2 to 14.2)
Obese	1.6 (-4.5 to 7.6)	0.1 (-9.3 to 9.5)	1.8 (-5.4 to 8.9)

Supplementary table 2.2. HIV status, ART use, and ART use by viral load and prevalence differences for ADL disability adjusting for confounders among HAALSI participants at baseline (N = 4452)

		Model 1*		**Model 2****
Predictor	Prevalence	**1+ADL Disability, Prevalence difference**	Prevalence	**1+ADL Disability, Prevalence difference**
HIV status				
Negative	11.7 (10.7 to 12.7)	Ref.	11.7 (10.7 to 12.7)	Ref.
Positive	12.8 (10.4 to 15.2)	1.1 (-1.5 to 3.7)	12.6 (10.2 to 14.9)	0.9 (-1.7 to 3.5)
ART status				
Non-user	8.3 (5.3 to 11.4)	Ref.	8.5 (5.4 to 11.5)	Ref
ART user	8.7 (6.6 to 10.7)	0.3 (-3.3 to 4.0)	8.8 (6.2 to 11.3)	0.2 (-3.5 to 3.9)
ART by viral load				
Suppressed ART user	8.1 (5.8 to 10.4)	Ref.	8.1 (5.8 to 10.4)	Ref.
Unsuppressed ART user	10.3 (6.0 to 14.7)	2.2 (-2.7 to 7.2)	10.3 (6.0 to 14.7)	2.2 (-2.7 to 7.2)
Non-user	8.3 (5.3 to 11.4)	0.2 (-3.6 to 4.0)	8.5 (5.4 to 11.5)	0.3 (-3.5 to 4.2)

*Adjusted for age, sex; **Adjusted for age, sex, education, father's occupation, country of origin, and alcohol ever use

Supplementary table 2.3. The independent association of age and BMI with ADL disability: predicted prevalence and prevalence differences of 1+ADL disability by different values of age and BMI among HAALSI participants at baseline

	1+ADL disability, prevalence difference	
Predictor value	**Model 1**	**Model 2**
Age (per SD change)	4.3 (3.6 to 5.0)	4.0 (3.2 to 4.8)
BMI		
Underweight	5.6 (1.1 to 10)	4.8 (0.6 to 8.9)
Normal	Ref.	Ref.
Overweight	0.01 (-2.1 to 2.1)	0.1 (-2.0 to 2.1)
Obese	0.9 (-1.3 to 3.1)	1.6 (-0.7 to 3.9)

*Adjusted for age (SD = 13 years), sex and HIV status; **Adjusted for age, sex, HIV status, education, father's occupation, country of origin and alcohol ever use

Chapter 3 : Is antiretroviral therapy alone sufficient to eliminate excess mortality related to Kaposi's sarcoma among HIV-infected adults in sub-Saharan Africa?

Background

Antiretroviral therapy (ART) has dramatically changed the face of HIV-associated Kaposi's sarcoma (KS). In both high-resource settings, where potent combination ART first emerged in 1996, and, more recently, in low-resource settings, ART has decreased KS incidence and improved population-level survival after KS diagnosis [34-36]. In fact, one of the most remarkable aspects of the introduction of ART were case reports of patients with KS who had their lesions shrink or completely resolve with ART alone, without any adjunctive therapy [37]. This formed the basis of the common practice in high-resource settings of using ART alone to treat KS that does not have immediately life-threatening complications [38, 39].

ART alone as initial therapy for KS is also practiced in low-resource settings, such as sub-Saharan Africa, but this is largely based upon the successes seen in high-resource settings and a practical response to the unaffordability of chemotherapy. The lack of direct evidence for this approach in sub-Saharan Africa is concerning given that the stakes can be viewed as considerably higher. In sub-Saharan Africa, the underlying endemicity of Kaposi's sarcoma-associated herpesvirus (the causative agent of KS) in the general population [40-42] has led to KS being common among all HIV-infected individuals [43], not just a sub-set as is seen in resource-rich settings such as the U.S, Europe, and Australia [44]. In recent data from sub-Saharan Africa, KS is the third most common cancer amongst all men and the fifth most common amongst all women [45, 46]. That the approach of ART alone for initial therapy of KS is successful in high-resource settings is not necessarily sufficient to justify it in Africa. The ample differences in KSHV strain [47, 48], HIV strains [49], human host, paradoxical responses to ART [50], and medical care infrastructure (e.g., availability of chemotherapy in case initial ART fails) between high-resource settings and sub-Saharan Africa cast doubt on the wisdom of extrapolating treatment approaches and suggest that direct data from Africa are needed.

To evaluate the strategy of initial therapy with ART alone for KS in sub-Saharan Africa, we studied survival in persons with AIDS-related KS initially treated with ART alone and a carefully assembled

comparable group of HIV-infected African adults without KS also initiated on ART. We sought to address whether initial use of ART alone is able to eliminate any excess mortality related to KS. While equivalent survival would justify continuation of the current approach of management, a residual mortality risk from KS would indicate that additional interventions are required over and above ART.

Methods

Study population and setting

Individuals with KS were participants in the Antiretrovirals for Kaposi's sarcoma (ARKS), a clinical trial performed at the Infectious Diseases Institute (IDI) in Kampala, Uganda (2007 to 2011) to assess whether ART regimens with protease inhibitors (PIs) were superior to regimens without PIs in treating KS. The participants were recruited from throughout Uganda and had biopsy confirmed KS without immediately life threatening complications. Those with indications for immediate chemotherapy such as mucocutaneous KS (bulky lesions ≥5cm diameter, ulcerated skin lesions, or oral lesion interfering with swallowing), suspected pulmonary or gastrointestinal KS (abnormal, and otherwise unexplained, chest x-ray, a positive occult blood stool test, or history of overt bleeding from the mouth or rectum), and lymphedema of the face or other body region resulting in symptoms or functional disability were excluded. Also, participants who had concurrent untreated opportunistic infections or other non-KS malignancy, or unexplained high temperature ($\geq 38.5^{o}$ C) were excluded.

Participants without KS were from the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort (2005-2015), a prospective study of HIV-infected adults designed to assess various outcomes following ART initiation. They were initiating ART for indications other than KS at the Immune Suppression Syndrome clinic in Mbarara, Uganda. A small number (n=16) who had KS that had been clinically diagnosed were excluded to avoid diagnostic heterogeneity and consequent measurement bias.

Both groups were followed from the time of ART initiation (time 0) until either death or administrative closure at 4 years. ARKS and UARTO were approved by institutional review committees at Makerere

University, MUST, the University of California San Francisco, and the Massachusetts General Hospital. The studies are also registered with formal prospective study registers.

Measurements

Primary predictor

The primary predictor was biopsy confirmed KS. Trained study personnel performed 4mm punch biopsies of two representative skin KS lesions on each patient, which were sent to the pathology laboratory for a histological diagnosis. If initial histology was uncertain, the slides were reviewed by a second pathologist. For few participants with only oral lesions, where a biopsy was deemed to pose substantial risk, a visual diagnosis confirmed by two study physicians sufficed.

Outcome

The primary outcome was mortality. As there is no national death index in Uganda, we established mortality through physically tracking patients in the community and obtaining reports from relatives and/or friends. For all the ARKS participants, and for UARTO participants who missed their quarterly appointments, community tracking was performed. A subject was considered lost as of their last contact with the study or clinic, if they were not known to have died, and no contact could be established with them for ≥180 days.

Predictor covariates

Socio-demographic and clinical information was collected using the same questionnaires for both groups. We measured socio-economic status using an asset index score [51, 52]. Clinical measurements included a history of serious opportunistic infections such as tuberculosis (TB), oro-esophageal candidiasis, and cryptosporidial diarrhea and the body mass index (BMI). A physical health summary score (PHS) was calculated for each participant from responses to the Medical Outcomes Survey-HIV questionnaire [53]. Laboratory studies were performed for both groups at the same laboratory (the Makerere John-Hopkins University collaboration core laboratory at IDI, Kampala) and included the hemoglobin level (Humacount, Human Diagnostics Worldwide, Wiesbaden, Germany); CD4+ T cell counts (FACSCount

System, BD Biosciences, San Jose, CA); and plasma HIV RNA levels (Roche Amplicor; Roche Diagnostics, Indianapolis, Indiana, USA).

Statistical analysis

We first used Kaplan Meier techniques to describe survival by group. We then performed multivariable-adjusted analyses using proportional hazards regression to determine the independent effect of being diagnosed with KS at ART initiation on survival. We adjusted for confounders of this relationship using a directed acyclic graph (DAG)-based approach [54]. To account for HIV disease progression, which is unmeasured, we adjusted for multiple proxies of the same variable that had been measured at ART initiation (**Figure 3.1**). Calendar time of ART initiation was one of the variables we had identified in the DAG as an important confounder. However, as the two groups were not overlapping on this variable, we performed one analysis adjusting for all measured confounders and proxies except calendar time, and another adjusting for all measured confounders and proxies including the calendar date of ART initiation. In addition to estimating hazard ratios of mortality by KS group, we calculated the adjusted absolute difference in the risk of mortality between the two groups at 4 years.

To check the assumptions of this analysis, we calculated scores of the propensity to be diagnosed with KS diagnosis by group based on all the covariates that were adjusted for; we examined these scores for positivity violations i.e., whether a substantial number of patients in either group had 0 or 100% probability of being diagnosed with KS. Also, we performed Schoenfeld tests and plotted the mortality hazard against follow-up time to assess proportionality of the hazard over time. As non-proportionality was found to be present i.e., mortality hazard changed substantially over time, we split follow-up time into two periods (0-1 year, and 1-4 years). Finally, we tested for the interaction of KS with CD4 T cell count and hemoglobin level.

After missing values were obtained from source documents whenever possible, we imputed any remaining missing values using iterative chained equations (ICE); we included in the imputation

equations variables with complete data (KS diagnosis, sex, history of tuberculosis, mortality, and observation time) and an interaction term between mortality and observation time. As we did not impute any missing outcomes, we performed sensitivity analyses assessing the impact that the limited number of losses to follow-up might have had on our results. We expected that loss to follow-up would not bias our inferences unless it acted differentially by exposure group. Hence, we assessed two extreme scenarios assuming death rates to be different by group in those lost to follow-up. In the first scenario, we assumed that all lost died only if they had KS; in the second, we assumed that all lost died only if they did not have KS. Mortality hazard ratios were recalculated under these assumptions. We also performed another sensitivity analysis assessing the impact of excluding participants, in both groups, who were in non-overlapping regions of the propensity to develop KS. All analyses were performed in Stata 13 (StataCorp, Texas, USA)

Results

Subject characteristics at ART initiation

From 2005 to 2013, we enrolled 224 participants with KS and 683 participants without KS. Enrollment for KS participants occurred in 2008-2010; enrollment for non-KS participants spanned a longer period (2006-2012). Median age was 34 years (IQR: 28-40) in both groups. The KS group had more males (56% versus 30%, $p<0.001$), lower physical health summary scores (median 53.2, IQR 36.4-58.2, versus 55.4, IQR 46.1-59.5, $p<0.001$), lower CD4+ T-cell counts (median 119, IQR 24-265/mm^3 versus 168 IQR 96-263, $P<0.001$), and higher plasma HIV RNA (median 5.4 IQR 5.0-5.6 $\log_{10}$ copies/ml versus 5.0, IQR 4.5-5.5 $\log_{10}$ copies/ml, $p<0.001$) (**Table 3.1**). None of the KS participants were considered to have clinically relevant visceral disease. Initial ART regimens were mainly tenofovir-based in the KS group (tenofovir with emtricitabine and ritonavir/lopinavir or efavirenz). This was unlike the no-KS group, where the majority received zidovudine-based regimens (zidovudine with lamivudine and nevirapine or efavirenz).

Unadjusted analysis

Participants were followed for a maximum of 4 years. For the KS group, median follow-up time was 2.4 years (IQR 1.3-3.3), with cumulative loss to follow up (in a competing risk analysis where mortality was the competing risk) estimated at 2% at 1 year and 6% at 4 years (**Figure 3.5**). In the group without KS, median follow-up time was 4.0 years (IQR 1.5-4.0), with cumulative loss to follow-up estimated at 8% at 1 year and 11% at 4 years. Cumulative mortality at 4 years was 30% in the KS group compared to 8.2% in the no-KS group (**Figure 3.2**). Mortality hazard varied across follow-up time being highest in the first year following ART initiation, and declining sharply afterwards, but remaining higher at all times in the KS group (**Figure 3.3**). In the unadjusted analysis, participants with KS had 5.2-fold (95% CI, 3.2-8.5, p<0.001) higher hazard of death in year 1, and 2.7-fold (95% CI, 1.3-5.7, p=0.008) higher hazard of death in years 2 to 4 compared to those without KS (**Table 3.2**).

Adjusted analysis

Adjusting for 12 measured confounders *(*age, sex, asset holding, date of ART initiation, history of TB, oro-esophageal candidiasis, and cryptosporidial diarrhea, the physical health summary score, BMI, hemoglobin, CD4+ T-cell count, and plasma HIV RNA level), participants with KS had 3.7-fold (95% CI, 2.1-6.7, p=<0.001) in year 1, and 2.2-fold (0.97-4.8, p=0.061) in years 2 to 4 higher hazard of death compared to participants without KS in a model not adjusting for calendar time (Table 2). After further adjusting for calendar time, the HR comparing participants with KS to those without KS increased to 5.0 (95% CI, 2.5-10.0, p=<0.001) in year 1, and 2.9 (95% CI, 1.2-7.0, p=0.020) in the years 2 to 4 period (**Table 3.2**).

Predictions of mortality risk from KS given ART

In estimating predicted risk of death given a KS diagnosis at ART initiation, a prototypical HIV-infected participant with KS had about 0.19 risk of death at 1 year (**Figure 3.4**). In comparison, a prototypical participant without KS had a much lower risk of about 0.04. At 4 years, the estimated risk of death for a

prototypical participant with KS was 0.29 compared to 0.083 for a prototypical participant without KS. This suggests a residual risk of 0.20 at 4 years of follow up.

Interactions

We tested for interactions between KS and CD4 and between KS and HB and found no evidence of such interactions (p=0.998, and p=0.972, respectively).

Sensitivity analyses

To assess the sensitivity of our results to losses to follow-up, we explored extreme mortality scenarios in those lost to follow-up. The first scenario assumed that among those lost to follow-up, all with KS died while none without KS died. In this scenario, the estimated HR increased to 5.9 (95% CI, 2.9-11.9, p=<0.001) in the first year of follow-up, and 3.3 (95% CI, 1.4-7.9, p=0.008) in years 2 to 4. In scenario 2, we assumed that among those lost to follow-up, none with KS died and all without KS died. In this scenario, the estimated HR decreased to 2.8 (95% CI 1.6-4.9, p= <0.001) in the first year, and 0.88 (95% CI, 0.42-1.8, p=0.72) in years 2 to 4. These extreme scenarios are unlikely in the real world, but, notably, even in the most extreme (and effectively most unlikely) scenario relevant to our inference where all lost to follow-up in the non-KS group are assumed to have died, while all lost to follow up the KS group survive, participants with KS remain at a substantially higher risk of death in the first year of follow up.

Additional sensitivity analyses, excluded patients whose propensity scores for a KS diagnosis given measured confounders was in regions of non-overlap (**Figures 3.6 and 3.7**). Specifically, we excluded participants with propensity scores ≤0.03, and those with propensity scores ≥0.88, where, based on a visual examination of histograms of the distributions of the propensity for having a KS diagnosis among KS and non-KS participants, regions outside these bounds did not have sufficient comparators in either group (≤4). This excluded from the analysis 441 participants from the no-KS group leaving only 242, and 99 participants from the KS group leaving only 125. A comparison of the remaining participants in a model adjusting for calendar time yielded largely similar results as the non-restricted analysis; the HR

comparing participants with KS to those without KS was 4.9 (95% CI, 1.9-12.6, p=0.001) in year 1, and 2.2 (95% CI, 0.68-7.3, p=0.183) in years 2 to 4.

Discussion

Previous studies have not accurately quantified the impact of ART on mortality from HIV-associated KS. In particular, for low-resource settings like SSA, where HIV-positive patients with early KS are often initially treated with ART alone, it is unclear whether ART alone can eliminate any excess mortality from KS and thus whether additional interventions over and above ART are required for such patients. Among HIV-infected adults initiating ART in Uganda, we tested the hypothesis that given ART, residual risk of mortality from KS becomes zero. Despite comprehensive adjustment to account for HIV disease progression at ART initiation, the risk of mortality following ART initiation remained about 5-fold higher in the first year among participants with KS compared to participants without KS. ART alone was not sufficient to eliminate excess mortality from KS suggesting the need for additional interventions over and above ART for patients with KS. Findings further suggest need for better prognostic classifications of KS since individuals with KS judged as low-risk at ART initiation had much higher mortality than comparable individuals without KS.

ART alone might fail to eliminate excess mortality from KS for several reasons. Among patients with KS, ART may have variable impact at the individual level. In particular, for patients in whom certain biological features of KS are present, e.g., excessive inflammation, additional treatments (e.g., anti-inflammatory agents) might be needed to supplement the beneficial effects of ART. Studies directly evaluating the role of inflammation in HIV-associated KS outcomes are still lacking, but KSHV, the causative agent of KS is known to be associated with inflammation [55]. Studies have also linked HHV8 replication with progressive KS disease [56] and suggest that KSHV-associated inflammation may increase immediately after ART [57]. Whereas previous studies from high-resource settings have reported substantial reductions in KS-related mortality following widespread ART use [34, 35, 58-60],

the population-level effects observed in these settings may have been partly influenced by non-ART factors (e.g., efficacious chemotherapy, radiotherapy and overall quality of health-care services. In previous studies from SSA, many of which did not adjust for as many confounders and are affected by high rates of loss to follow-up, mortality risk is consistently higher in patients with KS initiating ART than in other patients [61-67].

In our study, there was a precipitously high rate of mortality in the first year of ART initiation. The immune reconstitution syndrome (IRIS) is a possible explanation for this observation [68]. Although there are no confirmatory studies, some previous studies suggest that IRIS is more common and more strongly associated with mortality in African patients compared to patients in high-resource settings [69]. An alternative explanation is natural disease progression in absence appropriate adjunctive therapy. Assuming that chemo, which was available in ARKS, or its timing, were not sufficient, patients with a KS diagnosis might naturally rapidly decline and die in the first year of observation, despite ART [70].

Overall, mortality in our study was higher than what has been observed in high-resource settings, which, in addition to the precipitous death rates in the first year, may have other explanations. Diagnostic limitations in Africa probably leave a substantial burden of KS disease undetected at ART initiation (i.e., underdiagnosis and sub-optimal staging in the KS group) [71]. Further, the prognostic significance of well-known KS characteristics such as edema may be underestimated. In SSA, such risk factors could be indicative of worse underlying progression stage than in other settings [72]. The drivers of KS in sub-Saharan Africa and the population that gets KS may be different from other settings. For example, KS in sub-Saharan Africa is more generalized at the population level than in resource-rich settings [73-75]. There may thus be more heterogeneity in presenters, and generalized prognostic tools like the clinical criteria used to select participants into the KS group are less accurate and need to be more individualized. Finally, the lack of specific treatments for KS, when compared with other OIs which have OI-specific treatments, could make the survival of people with other OIs better compared to counterparts with KS. For example, patients with TB have access to treatments over and above ART; other OIs such as

esophageal candida and crypto diarrhea also often do not have specific treatments over and above ART, but these OIs may be more susceptible to ART alone than KS [76].

Our study has some limitations. We were unable to control for ART regimen composition. In theory, the ART regimens that were given to KS group may have been superior ─ more potent, and less toxic. However, we are not aware of any studies that have conclusively demonstrated superiority/inferiority of any of the ART regimens used. Even then, since there was higher mortality in the KS group, the bias resulting from this would be conservative, implying that the true HR is higher than what we observed. Adjunctive chemotherapy was, in general, accessible for the patients in the KS group, which is not the case for other KS patients initiating ART in sub-Saharan Africa. This also could imply that the observed mortality in the KS group is an underestimate of what actually happens to KS patients enrolling in routine care in sub-Saharan Africa. This also is a conservative bias, implying that the true HR may be higher than what we observed. The two populations are not strictly exchangeable because they were not sampled identically, and like in any observational study, there is potential for residual confounding. To minimize such biases we performed comprehensive adjustment using as many as possible of the surrogates of HIV disease progression at ART initiation. Moreover, measurements in both groups were done by the same laboratories and questionnaires to minimize systematic differences.

In conclusion, among patients initiating ART in Uganda, ART alone did not eliminate excess mortality from KS in presenters initially treated with ART alone, implying that additional interventions were required over and above ART, as well as better prognostic staging of KS. Our findings call for action to make efficacious adjunctive therapies available to all presenters with HIV-associated KS. What these adjunctive therapies are, other than those already known such as chemotherapy and radiotherapy remains the subject of future studies. Whether and how these therapies are used in individual patients, often a clinical decision, should also be subjected to further studies. Accordingly, we recommend studies examining the precipitous rates of mortality in KS patients in the first year following ART initiation. Such studies should attempt to separate the role of IRIS from that of natural disease progression in the

absence of sufficient treatment. This line of investigation may identify newer adjunctive therapies that are required for KS but are not yet being used. Future studies should also develop more accurate prognostic classifications for KS patients in sub-Saharan Africa.

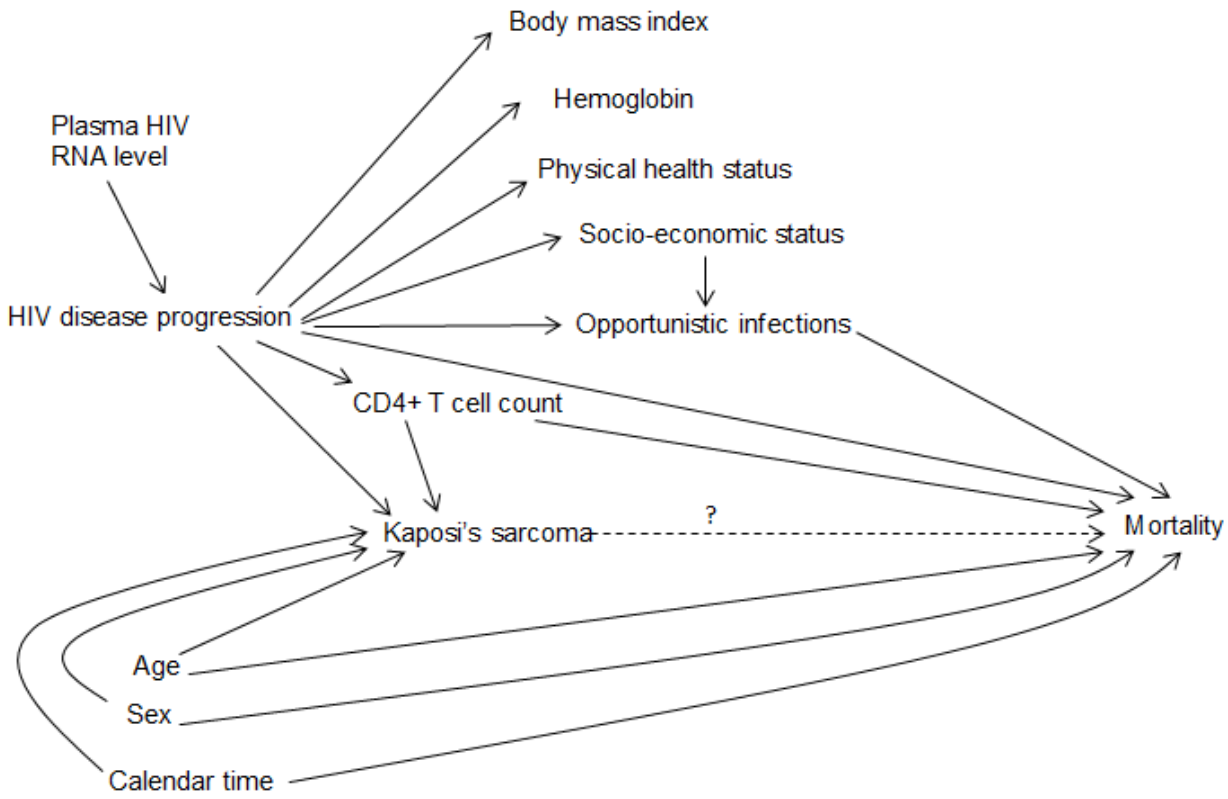


Figure 3.1. Directed acyclic graph (DAG) showing the hypothesized causal relationship between Kaposi's sarcoma (KS) and mortality amongst HIV-infected adults who are about to initiate antiretroviral therapy (ART). In this depiction, HIV disease progression is not directly measured but body mass index, hemoglobin, and physical health status summary are viewed as some of its proxy measurements along with socioeconomic status, opportunistic infections, and CD4+ T cell count. The present study seeks to determine whether a causal relationship between KS and mortality exists among patients treated initially with ART alone, thereby addressing whether ART alone is able to eliminate any excess mortality related to KS.

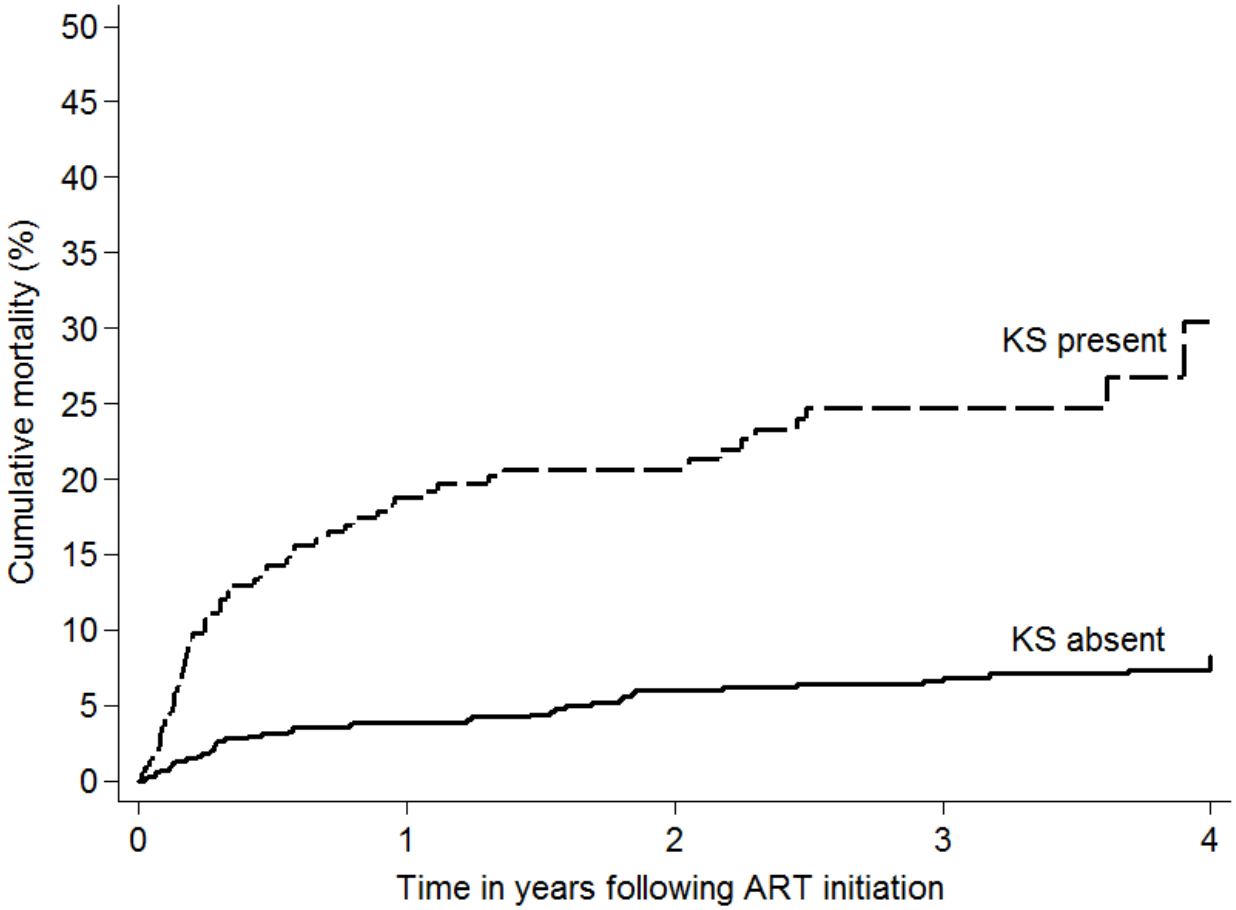


Figure 3.2. Unadjusted cumulative incidence of death over time amongst HIV-infected adults in Uganda following antiretroviral therapy (ART) initiation, by Kaposi's sarcoma (KS) status.

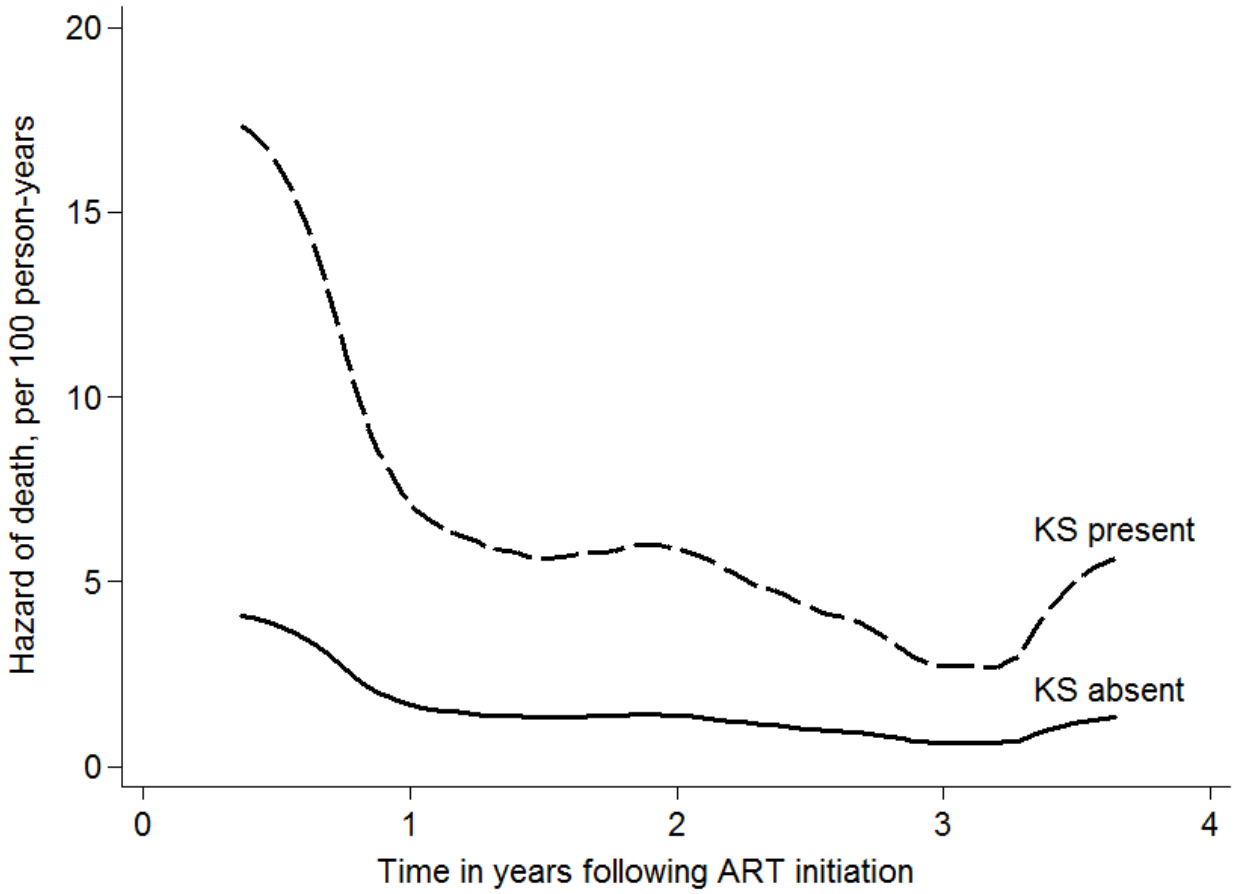


Figure 3.3. Smoothed unadjusted hazard of mortality amongst HIV-infected adults in Uganda following antiretroviral therapy (ART) initiation, by Kaposi's sarcoma (KS) status.

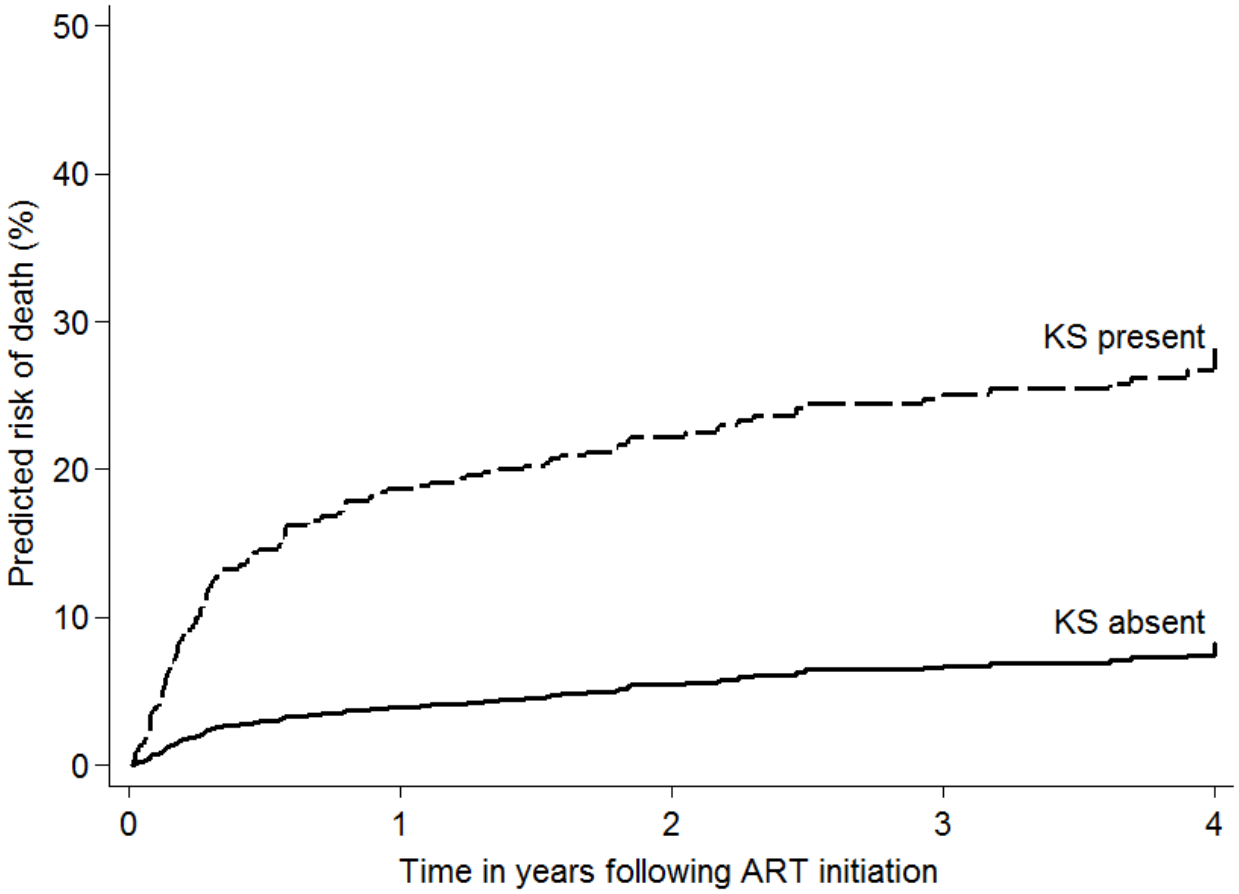


Figure 3.4. Predicted risk of death amongst HIV-infected adults in Uganda following antiretroviral therapy (ART) initiation, by Kaposi's sarcoma (KS) status. Estimates are adjusted for age, sex, asset holding, history of tuberculosis, history of cryptosporidial diarrhea, history of esophageal candidiasis, physical health summary score, body mass index, hemoglobin, CD4+ T cell count, plasma HIV RNA level and calendar date of ART initiation (Model 2). These predictions were obtained from a regression model that adjusted for all the listed covariates fixed on their population median values. The predictions represent what the expected risk of death following ART initiation would be in a prototypical patient from this population if they had KS versus if they did not.

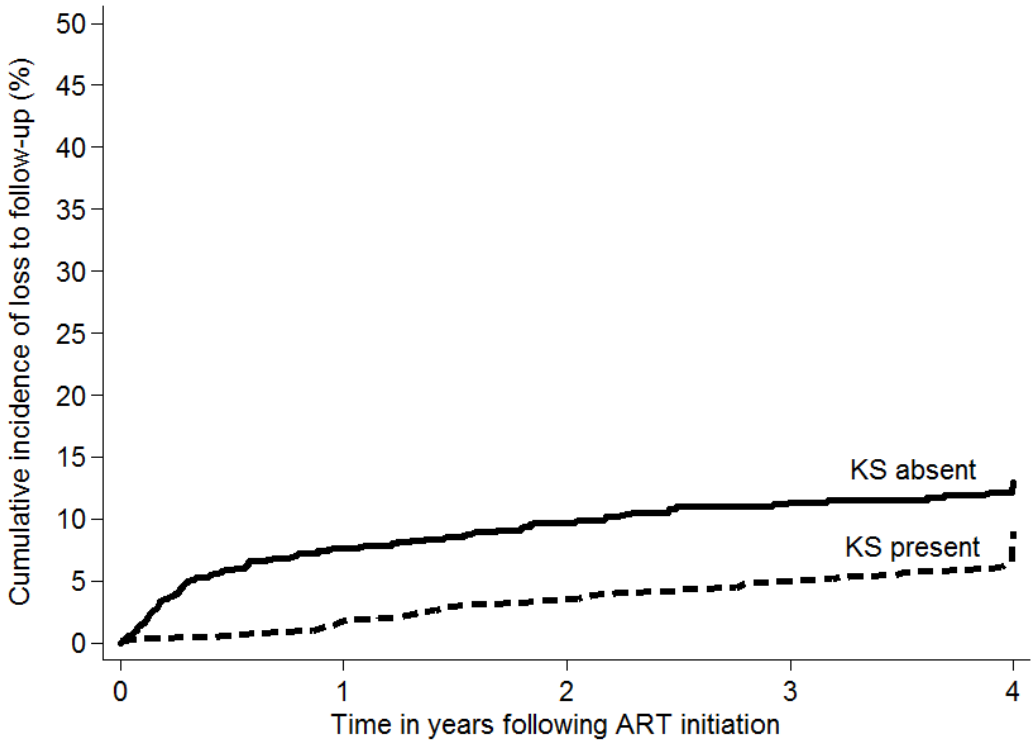


Figure 3.5. Cumulative incidence of becoming lost to follow-up amongst HIV-infected adults initiating antiretroviral therapy (ART) in Uganda, by Kaposi's sarcoma (KS) status.

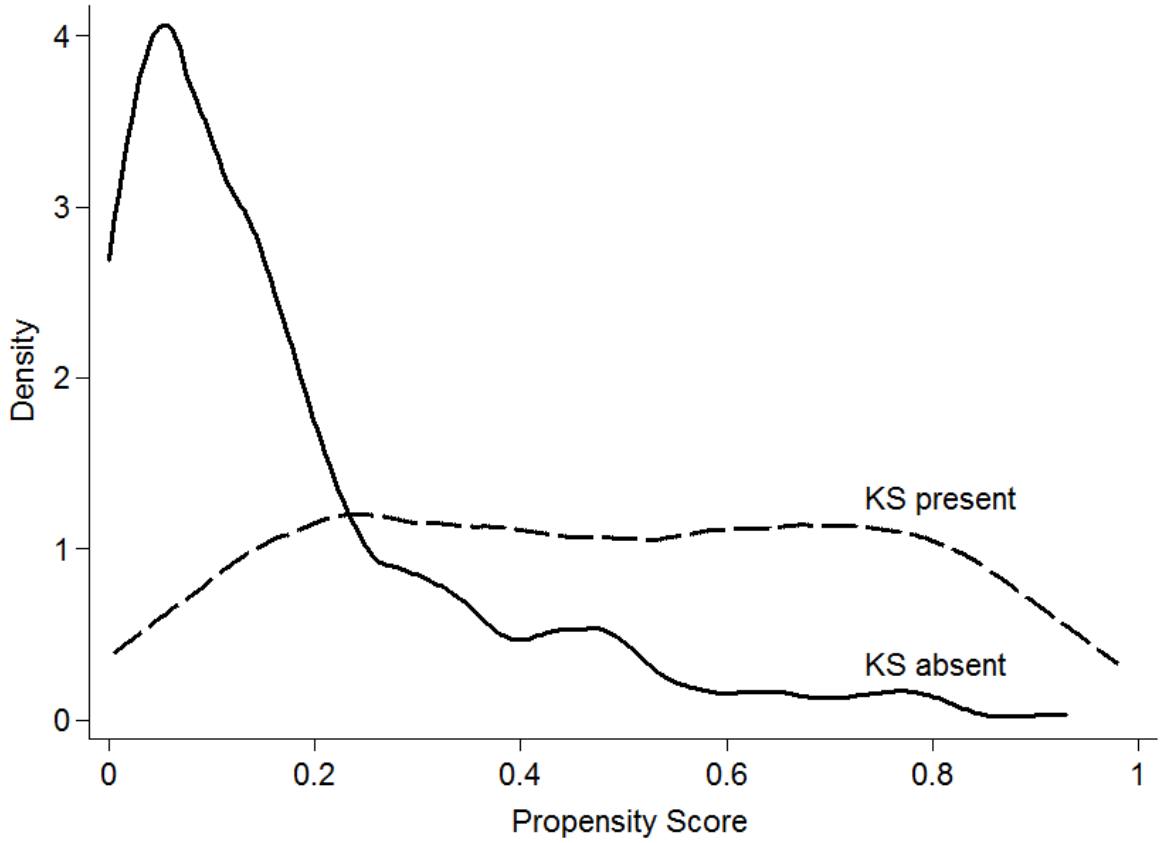


Figure 3.6. Distribution of propensity score of having a Kaposi's sarcoma (KS) diagnosis, according to KS status, amongst HIV-infected adults in Uganda (Model 1). Estimates are based on covariates that were adjusted for in multivariable model 1 (age, sex, asset holding, history of tuberculosis, history of cryptosporidial diarrhea, history of esophageal candidiasis, physical health summary score, body mass index, hemoglobin, CD4+ T cell count, and plasma HIV RNA level).

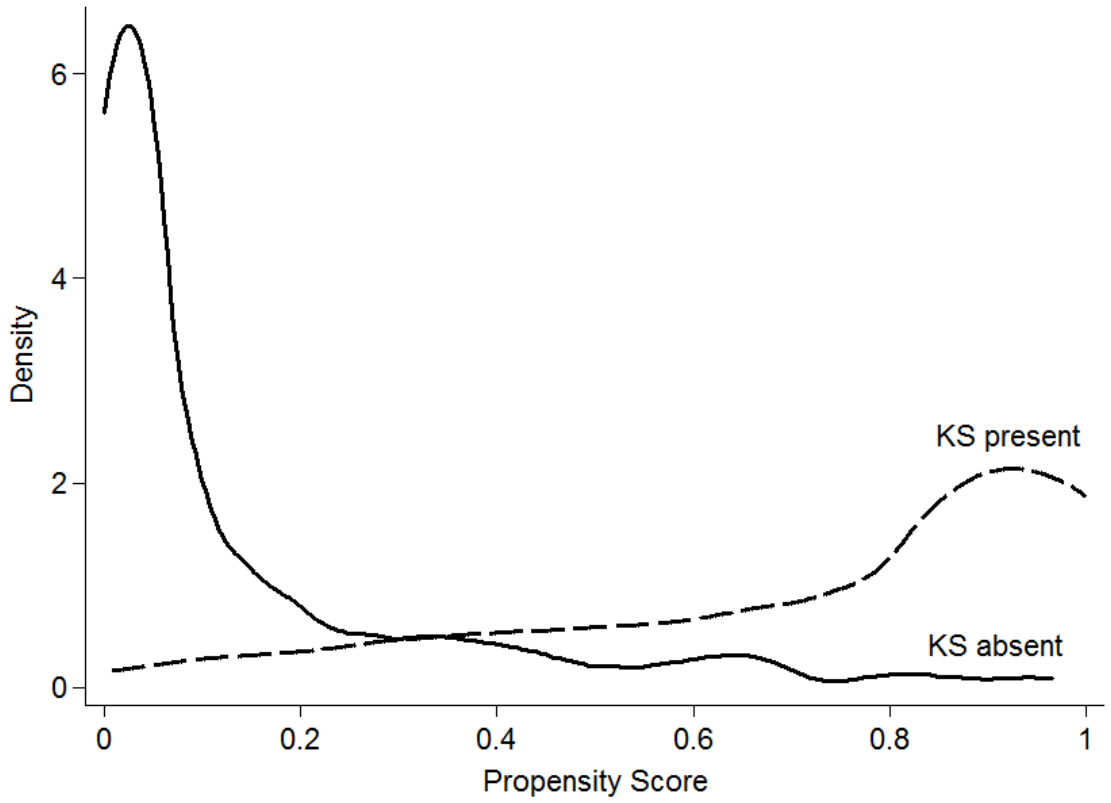


Figure 3.7. Distribution of propensity score of having a Kaposi's sarcoma (KS) diagnosis, according to KS status, amongst HIV-infected adults in Uganda (Model 2). Estimates are based on covariates that were adjusted for in multivariable model 2 (age, sex, asset holding, history of tuberculosis, history of cryptosporidial diarrhea, history of esophageal candidiasis, physical health summary score, body mass index, hemoglobin, CD4+ T cell count, and plasma HIV RNA level, in addition to calendar date of antiretroviral therapy initiation).

Table 3.1. Characteristics of HIV-infected adults in Uganda at time of antiretroviral therapy (ART) initiation, by Kaposi's sarcoma (KS) status.

Variable	KS Present (N=224)	KS Absent (N=683)
Age, years	34 (28 to 40)*	34 (28 to 40)
Male sex	56%	30%
Asset holding†	0.16 (-1.48 to 2.30)	-1.41 (-2.29 to -0.20)
Tuberculosis, history of	12%	9.2%
Cryptococcal meningitis, history of	0.45%	1.2%
Oro-esophageal candidiasis, history of	4.5%	13%
Cryptosporidial diarrhea, history of	1.4%	8.6%
Physical health score‡	53.2 (36.4 to 58.2)	55.4 (46.1 to 59.5)
Body mass index, kg/m^2	21.4 (19.4 to 23.1)	21.2 (19.5 to 23.8)
Hemoglobin, g/dl	11.8 (10.5 to 13.2)	12.6 (11.2 to 14.0)
CD4+ T cells/µl	119 (24 to 265)	168 (96 to 263)
HIV RNA, log$_{10}$ plasma copies/ml	5.4 (5.0-5.6)	5.0 (4.5-5.5)
Year of ART initiation		
2005	-	7.6%
2006	-	18%
2007	8.9%§	25%
2008	30%	14%
2009	31%	5.9%
2010	16%	1.5%
2011	1.3%	13%
2012	-	12%
2013	-	2.8%

* Median (interquartile range) unless otherwise indicated
† From the Filmer-Pritchett index, a marker of socio-economic status [51]
‡ From the Medical Outcomes Study-HIV survey [53]

Table 3.2. Effect of Kaposi's sarcoma (KS) diagnosis on subsequent mortality following initiation of antiretroviral therapy (ART) amongst HIV-infected adults in Uganda.

Time after ART initiation	KS diagnosis	Unadjusted Model		Adjusted Model 1*		Adjusted Model 2†	
		Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value	Hazard Ratio* (95% CI)	P value
Year 1	Absent	Ref.		Ref.		Ref.	
	Present	5.2 (3.2-8.5)	<0.001	3.7 (2.1-6.7)	<0.001	5.0 (2.5-10.0)	<0.001
Year 2-4	Absent	Ref.		Ref.		Ref.	
	Present	2.7 (1.3-5.7)	0.008	2.2 (0.97-4.8)	0.061	2.9 (1.2-7.0)	0.020

*Adjusted for age, sex, asset holding, history of tuberculosis, history of cryptosporidial diarrhea, history of esophageal candidiasis, physical health summary score, body mass index, hemoglobin, CD4+ T cell count, and plasma HIV RNA level.
†Adjusted for the same set of confounders as model 1 in addition to calendar date of ART initiation.

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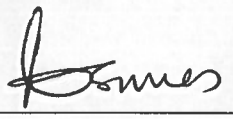

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