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Mortality and immunological recovery among older adults on antiretroviral therapy at a large urban HIV clinic in Kampala, Uganda

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Abstract

Background—We describe older (> 50 years) HIV-infected adults after ART initiation, evaluating immunological recovery by age category, considering individual trajectories based on the pre-treatment CD4. We also describe mortality on ART and its risk factors by age category including the contribution of poor immunological recovery at a large urban clinic in Kampala, Uganda.

Methods—We performed a cohort analysis of adult (>18 years) HIV-infected patients who initiated ART between January 1, 2004 and January 3, 2012. Immunological response was evaluated using mixed-effects linear regression. We described mortality using Kaplan Meier survival methods analyzing for risk factors of mortality using multivariate Weibull survival regression stratified by age category.

Results—Among 9,806 individuals who initiated ART, mean age was 37 years (S.D 8.8), average follow-up 5.7 years (S.D 1.7) and median baseline CD4 was 115 cells/mm³ (IQR; 42–184). Adults <50 years had on average a higher CD4 increase of 45 cells/mm³ (95% CI; 17, 72, $p=0.001$) compared to counterparts aged ≥ 60 years. Mortality was highest among older adults compared to younger counterparts. Only CD4 count <100 cells/mm³ after 1 year on ART and a CD4 count less than baseline were associated with a statistically significant higher rate of death among older adults.

Conclusion—Older adults had a slower immunological response which was associated with mortality, but this mortality was not typically associated with opportunistic infections. Future

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CONFLICTS OF INTEREST:

None

steps would require more evaluation of possible causes of death among these older individuals if survival on ART is to be further improved.

Keywords

Mortality; Immunological response; >50 years; HIV/AIDS; Sub-Saharan Africa; Antiretroviral therapy

INTRODUCTION

The scale-up of antiretroviral therapy (ART) is one of the largest global public health interventions ever implemented, almost reaching 10 million HIV-infected adults in sub-Saharan Africa (SSA) ¹. Consequently, these adults are now unlikely to die from opportunistic infections that typified the pre-ART era hence live longer. However, ART era studies from resource-rich settings have indicated that older adults with HIV might experience distinct challenges compared to younger counterparts. For instance, older adults were found to have; advanced disease at diagnosis, faster progression to AIDS, and higher mortality^{2,3}. Besides, older individuals had a blunted immunological response to ART⁴⁻⁷, higher risk of ART related toxicities ^{2,8-10} and a greater burden of cardiovascular, endocrine and oncologic co-morbidity ¹⁰⁻¹⁶. Other studies, conversely, suggest that these older HIV-infected patients may not be any different from younger counterparts particularly in terms of immune recovery ^{7,13,17}, viral suppression^{2,6,17,18} or clinical disease progression⁶. Notably, data from resource-rich countries may not accurately reflect the experience of older individuals in resource-poor settings, especially SSA, given the appreciably different HIV-infected population characteristics, spectrum of opportunistic infections, in addition to initiation of ART at much lower CD4 counts, all within a context of higher HIV/AIDS prevalence.

Recently, there are some studies from SSA ¹⁹⁻²³. These studies have reported on various aspects, mainly mortality^{19,20,22}, with some reporting on immunological response ²⁰. Studies reporting on immunological recovery among both older and younger adults used different definitions for suboptimal immunological response²⁴⁻²⁶. Importantly, approaches that illustrate patient-specific change in CD4+ T-cell count accounting for CD4 at ART initiation have been rarely used. This is vital not to misclassify patients as having suboptimal immunological response yet they have had a slow but appreciable rise in CD4 albeit from a low baseline. Patient specific trajectory in CD4+ T-cell change is critically dependent on CD4 at ART start^{27,28}. Additionally, most of these studies evaluating immunological recovery were done among younger patients. Further, the role and pattern of immunological recovery in relation to mortality among older HIV/AIDS adults on ART has been largely unexplored. Importantly, other risk factors for mortality among older adults on ART have also not been fully evaluated.

From the Adult Infectious Diseases Clinic (AIDC) in Kampala, Uganda, we describe older adults with HIV on ART, evaluating immunological recovery by age category while accounting for individual CD4 change based on the pre-treatment measurement. We also

describe mortality and its risk factors by age category, evaluating the association with poor immunological recovery.

METHODS

Study Site and materials

The AIDC is part of the Infectious Diseases Institute (IDI), at the College of Health Sciences, Makerere University and is found within the Mulago national referral Hospital complex in Kampala, Uganda. Since 2002, the AIDC has offered free outpatient HIV/AIDS care to over 25,000 patients. Currently, 10,715 patients are actively in care, 7,355 of whom are on ART: with 6,510 on first-line and 845 are on second-line. Individuals also receive free cotrimoxazole prophylaxis, on-going counseling, and reproductive health services at no cost to the patient.

Study design, inclusion and exclusion criteria

We performed a cohort analysis of adult (>18 years) HIV-infected patients who initiated ART between January 1, 2004 and January 3, 2012. From ART initiation, we followed previously ART naïve patients who had more than one follow-up visit using clinic data. We retrieved data on patients' demographic information, WHO clinical staging, ART toxicity, opportunistic infections, anthropometric measurements, CD4 counts and vital status.

Data Collection

Initially, important patient data captured during clinic visits were recorded in the patient chart then manually entered into an in-house electronic database²⁹. The data were routinely checked for consistency and updates to data were made using queries usually generated during the same day that the data were collected. Also, additional updates to vital status (via patient tracking in the community) and important outcomes including opportunistic infections (OIs): particularly tuberculosis (TB) and Kaposi's sarcoma (KS) were made. Validation of TB and KS diagnoses were done by review of patient charts and laboratory records.

ART therapy

During the study period, ART management at the AIDC followed the Uganda National Antiretroviral therapy guideline³⁰. Typically, first-line regimen at IDI contains a combination of two Nucleoside Reverse Transcriptase inhibitors: lamivudine or emtricitabine and zidovudine or tenofovir and a Non Nucleotide reverse transcriptase inhibitor (NNRTI); efavirenz or nevirapine. Patients initiated on stavudine containing first-line regimens between 2004 and 2008 were all switched to tenofovir or zidovudine by the end of 2009. Second-line regimens usually involve substitution of the NNRTI for a Protease Inhibitor (PI), preferably atazanavir or lopinavir /ritonavir. ART therapy is monitored with CD4+ T-cell counts usually every 6 months. HIV-RNA levels are only measured when a clinician deems it necessary especially with suspected treatment failure. Patients return either monthly or every 3 months if stable for ART refills depending on adherence profile or response to therapy. Toxicity to ART was assessed based on known side-effect profiles of drugs as reported by patients and recorded by clinicians during routine visits.

CD4+ T-cell counts

Blood samples for CD4+ T-cell measurements are analyzed at the Makerere University-John's Hopkins University (MUJHU) Core laboratory housed within IDI, which also maintains accreditation by the College of American Pathologists. For this analysis we defined baseline CD4+ T cell count as the most recent test done within 3 months prior to or one week after ART was started.

Vital status

Vital status (death, transfer-out, loss to follow-up) data were obtained from the database that is continuously updated through feedback from relatives and/ or active tracking efforts in the community for those lost to follow-up. For individuals whose date of death was unknown and yet were known to have died, we used the last clinic visit as the possible date of death since most of them were very ill by the time they dropped out of care. Loss to follow-up was defined as having no clinic visit 3 months after the expected return date to clinic.

Statistical analysis

We describe demographic data for individuals aged < 50 years in comparison to those aged 50-59 years and those aged ≥ 60 years. We made group comparisons using chi square test for trend, Wilcoxon rank-sum test and Analysis of Variance (ANOVA) for mean comparisons of continuous variables as necessary.

Impaired immunological recovery was evaluated using previously published definitions of failure to achieve a CD4+ T-cell count > 100 after 1 year on ART and having a CD4+ T-cell count < baseline after 1 year on ART^{25,26}. We then applied multilevel mixed-effects linear regression to predict the linear trend in CD4+ T-cell increase after ART initiation in relation to age categorized as <50, 50-59, and ≥ 60 years after adjustment for pre-treatment (baseline) CD4, WHO disease stage, sex, and opportunistic infections at ART initiation. The covariates used in this model were chosen based on our biological understanding of the system. In this model we account for clustering by individual and account for time on ART as a splined interaction. We obtained and graphed the predicted mean CD4 change from this linear model (Figure 2).

Using Kaplan-Meier survival analysis we compared mortality between individuals aged < 50 years to those aged ≥ 50 years. We also performed a sensitivity analysis for mortality considering those lost to follow-up as dead (data not presented). We assess risk factors for mortality, comparing individuals aged <50 years to those ≥ 50 years using multivariate Weibull survival analysis due to the dependency of the hazards of mortality on time since ART start. We then stratified the models by 2 age categories (<50 years and ≥ 50 years) to compare risk factors for death between age groups. We adjusted for known risk factors for death which included; baseline CD4, KS at ART start, TB status at ART start, sex, and WHO disease stage. We tested for the appropriateness of the Weibull survival regression using the gamma distribution for which the null hypothesis that $X=1$ was not statistically significant with $p=0.5$. All analyses were performed using STATA (StataCorp. STATA 12, College Station, Texas 77845 USA).

Ethical Approval

The study and use of data were reviewed and accepted by the Scientific Review Board of the Infectious Diseases Institute, the Institutional Review Board of Makerere University and the Uganda National Council for Science and Technology (HS 683).

RESULTS

Cohort description

We followed a total of 9,806 individuals who initiated ART during the study period and contributed 33,683 person-years of follow-up. Mean age at ART initiation was 37.0 years (S.D $\pm$ 8.8) and mean follow-up was 5.7 years (S.D $\pm$ 1.7) from ART initiation. Of all the participants, the majority were female, 64.8% (6,351), though males predominated among older adults (61.4% for >60 years) (Table 1). We found some differences between groups based on baseline WHO clinical stage, tuberculosis (TB) status and Kaposi's sarcoma (KS) prevalence at ART initiation, with younger patients being more likely to suffer from TB while older patients were more likely to have KS, though these weren't statistically significant (Table 1). Overall the mean BMI and regimen at ART initiation were similar across age groups (Table 1). The median CD4 at ART initiation was 115 cells/ μ l (IQR: 42-184) with older individuals having higher median CD4+ T-cells, 142 (IQR: 76-196) (50-59 years) and 156 (IQR: 80-196) cells/ μ l (< 60 years) compared to younger counterparts; CD4 112 cells/ μ l (IQR: 40-183), p <0.001. Additionally while on ART, older individuals were more likely to have 2 or more ART related toxicities: 13.2% (50-59 years), 15.2% (< 60 years) compared to 11.2% (<50 years), p =0.021.

At the end of follow-up, more participants <50 years were on second-line regimen compared to older patients but this was not statistically significant, p =0.110 (Table 2). Initially, older patients (< 50 years) comprised 7.9% (774) of the total cohort population but this proportion increased to 16.7% (1641) at cohort closure, with 662 individuals becoming 50 years old while on ART during the follow-up period. This represents a cumulative incidence of reaching age>50 years of 1.1% (95% CI: 0.97, 1.4) after 1 year on ART and 10.4% (95% CI: 9.5, 11.4) after 6 years.

Immunological recovery

From the mixed effects linear regression as depicted in figure 2, prior to 2 years on ART, the mean increase in CD4 for patients aged 50-59 was 6 cells/ mm^3 (95% CI: -8, 19, p =0.400) higher than for patients <50 years, while for patients $\geq$ 60 years it was 45 cells/ mm^3 (95% CI: 17, 72, p =0.001) lower than for participants aged <50 years (Figure 2). However, after 2 years on ART, compared to those <50 years, the average CD4 change for patients 50-59 years was lower by 11 cells/ mm^3 (95% CI: -35, 13, p =0.4), and lowest by 80 cells/ mm^3 (95% CI: 27, 131; p =0.003) for those $\geq$ 60 years (Figure 2). Further, after 2 years on ART, 0.26% of those aged <50 years were predicted to still have a CD4 <200 cells/ mm^3 , while the proportion was almost 10 times higher (2.6%) among those $\geq$ 60 years. Using previously published definitions, a higher proportion of older patients $\geq$ 60 years (8.3%) had CD4 < 100 after 1 year on ART compared to 6.5% and 8.0% for 50-59 and <50 years respectively,

$p=0.380$. Twelve percent of those ≥ 60 years had $CD4 < \text{baseline}$ after 1 year on ART compared to 8.6% for 50-59 and 7.6% for < 50 years, $p=0.070$.

Mortality

Overall, 778 individuals died during follow-up with a higher proportion of deaths occurring among older participants: 12.2% (50-59 years) and 19.6% (≥ 60 years) vs. 7.4% (< 50 years), $p<0.001$. Sixty nine percent of the deaths occurred within the first 12 months on ART, while 31% occurred thereafter. Whereas most individuals aged < 50 years (70%) and 50-59 years (69%) died within the first 12 months on ART, most of those aged ≥ 60 years (61.3%) died over 12 months after starting ART. Cumulative incidence of mortality in the first year on ART was 5.7% (95% CI: 5.3, 6.3) while at 3 years it was 9.3% (95% CI: 8.7, 10.0) and 10.2% (95% CI: 9.5, 11.0) at 7 years. Generally, older individuals had a higher cumulative mortality than their younger counterparts (Figure 1).

Overall mortality rate was 2.3 (95% CI: 2.1, 2.5) per 100 person-years. This rate was highest in the first 3 months on therapy, at 360 (95% CI: 320, 400) per 100 person-years and reduced to 0.74 (95% CI: 0.65, 0.84) per 100 person-years after one year on ART. Mortality also reduced over calendar time from 1,000 (95% CI: 620, 1700) per 100 person-years in 2004 to 0.24 per 100 person-years (95% CI: 0.19, 0.31) in 2011. Mortality was highest among both groups of older adults; at 6.5 per 100 person-years (95% CI: 4.6, 9.3) for those ≥ 60 years, and 3.6 per 100 person-years (95% CI: 2.9, 4.5) for 50-59 years compared to 2.2 per 100 person-years (95% CI: 2.0, 2.3) for the < 50 years old.

Risk Factors for mortality

In the univariate survival analysis, $BMI < 19 \text{ Kg/M}^2$, failure to achieve $CD4 \text{ count} > 100 \text{ cell/mm}^3$ after 1 year on ART and a $CD4 \text{ count}$ less than baseline after 1 year on ART were associated with a statistically significant higher risk of death for both older and younger individuals (Table 3). In addition, male sex, WHO clinical stage 3 or 4, baseline $CD4 \text{ count} < 100$, TB, and KS at ART initiation were associated with a statistically significant higher risk of death only among younger individuals (< 50 years) (Table 3). In the adjusted analysis, only failure to achieve $CD4 \text{ count} > 100$ after 1 year on ART and a $CD4 \text{ count} < \text{baseline}$ after 1 year on ART were still associated with a statistically significant higher risk of death for both older and younger individuals. Additionally, $BMI < 19 \text{ Kg/M}^2$, WHO clinical stage 4, and $CD4^+ \text{ T-Cell counts} < 100$ at ART start were associated with a statistically significant higher risk of death only among younger individuals (Table 3). In sensitivity analyses assuming all those lost to follow-up as dead, point estimates for both univariate and multivariate analyses showed similar statistically significant qualitative associations though with slightly attenuated point estimates (not presented).

DISCUSSION

Widespread use of ART in Africa is changing the face of the HIV infected population in care. As more adults age while on ART; the need to clarify the unique challenges this imposes on HIV care gives increases as well. Importantly, in this study we note that more patients over calendar-time were making it to their 50th birthday, with a doubling in the

proportion of older adults over 6 years. This is not surprising since ART is increasingly more available, and its attendant benefits accruing.

Notably, we found distinct demographic differences between age groups. For instance, the proportion of males compared to females was higher among the older adults. This has been noted previously^{19,20,22} and the explanation this is probably a result of older men having younger women as intimate partners. Partially, this could be supported by the higher proportion of females (almost two-thirds) among younger patients. However, this demographic observation could be temporary and is thus likely to change as more young women (majority of HIV-infected patients) approach their 50th decade while on ART.

Contrary to some previous publications suggesting that older HIV-infected patients were more likely to have advanced HIV disease^{2,3} at ART initiation, we found that older patients were less likely to have advanced HIV disease based on, TB diagnosis status, CD4 counts and WHO clinical stage at ART initiation. Since TB is the most common opportunistic infection in this population³¹ and it's predominant among younger individuals³², this could in part explain this observation since older adults had a lower proportion of TB at ART initiation. We acknowledge that while clinicians have been trained to stage patients systematically and look for OIs, this process can be more subjective than objective and hence may have under reported OIs in the database. Nonetheless, both the clinical and immunological data are in tandem to suggest that older patients were generally in better health at ART initiation than younger counterparts.

Despite having a higher median CD4 at ART initiation, we noted that patients who initiated ART aged 50 years and above generally had a slower CD4 increase. In fact, the proportion of those with a CD4 <200 cells/ μ l after 2 years on ART was 10-fold higher among the older individuals (>60 years). This phenomenon has previously been recognized.^{33,34} It has been postulated that the slower CD4 increase among older individuals especially after 1 year on ART is largely a result of depleted thymic function that usually determines the second phase of CD4 restoration. We noted that the initial increase in CD4 within the first year on ART was similar between all age groups. This initial and usually rapid CD4 increase is principally attributed to cell redistribution from lymphoid tissue and also peripheral memory T-cell proliferation^{35,36}. Conversely, the thymus dependent second phase, which produces naïve T-cells declines as the thymus reserve diminishes with age³⁷. Consequently, older individuals are more likely to have low thymus reserve and hence poorer long term CD4 restoration as determined in our study.

As has been noted elsewhere in SSA³⁸⁻⁴⁰, mortality while on ART among newly initiated individuals was highest early on during therapy and then reduced thereafter. Besides, the mortality rate among older patients was higher than for the younger individuals overall. We noted that while mortality among the younger individuals almost leveled off after 1 year on ART, older adults continued to die thereafter albeit at much lower rate. Thus the much older patients (>60 years) continued to die more than the younger patients.

Indeed in any given population the risk of death is highest among older individuals and understanding risk factors for death is important in facilitating further efforts to reduce

mortality for patients on ART. Among younger individuals on ART, death was associated with most of the previously known AIDS related risk factors like low BMI, WHO clinical stage 3 and 4, and CD4 <100 cells at ART start. These factors have been linked to AIDS defining illnesses (ADIs) like TB, KS and cryptococcal meningitis that are associated with early mortality on ART³⁸⁻⁴⁰. In the unadjusted analysis, TB and KS diagnosis at ART initiation was associated with mortality. Therefore most of the deaths among individuals aged <50 years could be related to possible ADIs. Nonetheless, among older adults we didn't find a strong association between mortality, low BMI, WHO clinical stage 3 and 4, and CD4 <100 cells at ART start. Mortality among older adults was only associated with suboptimal immunological response defined as failure to achieve CD4 >100 cells after 1 year on ART and a CD4 < baseline after 1 year on ART but not associated with ADIs. Poor immunological recovery has been found to be associated with non-AIDS deaths^{34,41} as is suggested in these data. Among patients with poor immunological recovery, the non-AIDS conditions such as cardiovascular disease^{34,42,43}, non AIDS related malignancies⁴⁴ and liver disease⁴⁵ have been reported. However, data regarding these events were unavailable from our cohort and the ascertainment of these outcomes is still challenging in a resource poor setting, hence we can only hypothesize at this point in time.

Our findings should be interpreted within the context of some limitations. First, not all patients had HIV-RNA levels measured and when available they were not done regularly to enable us determine the degree of HIV-RNA viral suppression especially among those we suspected to have a poor immunological response. Therefore for the patients who had impaired immunological recovery we suspect that some of them might as well have had poor virological response. Recently though, self-reported adherence in our cohort was reported at 99.8%, making this less likely⁴⁶. Further, while we had a small proportion of loss to follow-up (about 15%), it could have led to informative censoring but sensitivity analyses that account for this showed some quantitative differences in point estimates but no qualitative differences. We also had some missing data which could have had some impact on our results but we believe that this impact was lessened by the large database since missingness was likely completely random. Finally, our analytical models are still likely to have some unmeasured confounding in part due to lack of HIV-RNA data and missing data.

Conclusion

At this clinic in SSA, older adults had the slowest increase in CD4, possibly leading to poor immunological recovery, and they also had a generally higher risk of death after ART start. While mortality among younger adults was associated with traditionally known ADIs in addition to poor immunological response, among older adults it was only associated with the latter. ADIs were not associated with mortality among older adults hence suggesting that the poor immunological recovery could be operating via alternative mechanisms to lead to death among older adults. Therefore it's imperative to better evaluate the mechanisms by which poor immunological recovery could lead to death among these older adults on ART in Africa so as to appropriately stem further mortality among adults on long term ART.

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REFERENCES

1. Global update on HIV treatment 2013: Results, impact and opportunities. <http://www.who.int/hiv/pub/progressreports/update2013/en/>
2. Cuzin L, Delpierre C, Gerard S, Massip P, Marchou B. Immunologic and clinical responses to highly active antiretroviral therapy in patients with HIV infection aged >50 years. *Clin Infect Dis*. Sep 1; 2007 45(5):654–657. [PubMed: 17683004]
3. Ferro S, Salit IE. HIV infection in patients over 55 years of age. *J Acquir Immune Defic Syndr*. 1992; 5(4):348–353. [PubMed: 1548571]
4. Goodkin K, Shapshak P, Asthana D, et al. Older age and plasma viral load in HIV-1 infection. *AIDS*. Jan 1; 2004 18(Suppl 1):S87–98. [PubMed: 15075503]
5. Grabar S, Kousignian I, Sobel A, et al. Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. *AIDS*. Oct 21; 2004 18(15):2029–2038. [PubMed: 15577624]
6. Greenbaum AH, Wilson LE, Keruly JC, Moore RD, Gebo KA. Effect of age and HAART regimen on clinical response in an urban cohort of HIV-infected individuals. *AIDS*. Nov 12; 2008 22(17):2331–2339. [PubMed: 18981772]
7. Navarro G, Nogueras MM, Segura F, et al. HIV-1 infected patients older than 50 years. PISCIS cohort study. *J Infect*. Jul; 2008 57(1):64–71. [PubMed: 18572247]
8. Knobel H, Guelar A, Valdecillo G, et al. Response to highly active antiretroviral therapy in HIV-infected patients aged 60 years or older after 24 months follow-up. *AIDS*. Aug 17; 2001 15(12):1591–1593. [PubMed: 11505000]
9. Manfredi R, Chiodo F. A case-control study of virological and immunological effects of highly active antiretroviral therapy in HIV-infected patients with advanced age. *AIDS*. Jul 7; 2000 14(10):1475–1477. [PubMed: 10930176]
10. Shah SS, McGowan JP, Smith C, Blum S, Klein RS. Comorbid conditions, treatment, and health maintenance in older persons with human immunodeficiency virus infection in New York City. *Clin Infect Dis*. Nov 15; 2002 35(10):1238–1243. [PubMed: 12410484]
11. Biggar RJ, Kirby KA, Atkinson J, McNeel TS, Engels E. Cancer risk in elderly persons with HIV/AIDS. *J Acquir Immune Defic Syndr*. Jul 1; 2004 36(3):861–868. [PubMed: 15213571]
12. Manrique L, Aziz M, Adeyemi OM. Successful immunologic and virologic outcomes in elderly HIV-infected patients. *J Acquir Immune Defic Syndr*. Jul 1; 2010 54(3):332–333. [PubMed: 20571414]
13. Orlando G, Meraviglia P, Cordier L, et al. Antiretroviral treatment and age-related comorbidities in a cohort of older HIV-infected patients. *HIV Med*. Nov; 2006 7(8):549–557. [PubMed: 17105515]
14. Oursler KK, Goulet JL, Leaf DA, et al. Association of comorbidity with physical disability in older HIV-infected adults. *AIDS Patient Care STDs*. Nov; 2006 20(11):782–791. [PubMed: 17134352]
15. Silverberg MJ, Leyden W, Horberg MA, DeLorenze GN, Klein D, Quesenberry CP Jr. Older age and the response to and tolerability of antiretroviral therapy. *Arch Intern Med*. Apr 9; 2007 167(7):684–691. [PubMed: 17420427]

16. Skiest DJ, Rubinstien E, Carley N, Gioiella L, Lyons R. The importance of comorbidity in HIV-infected patients over 55: a retrospective case-control study. *Am J Med.* Dec. 1996; 101(6):605–611.
17. Tumbarello M, Rabagliati R, De Gaetano Donati K, et al. Older HIV-positive patients in the era of highly active antiretroviral therapy: changing of a scenario. *AIDS.* Jan 3; 2003 17(1):128–131. [PubMed: 12478081]
18. Nogueras M, Navarro G, Anton E, et al. Epidemiological and clinical features, response to HAART, and survival in HIV-infected patients diagnosed at the age of 50 or more. *BMC Infect Dis.* 2006; 6:159. [PubMed: 17087819]
19. Bakanda C, Birungi J, Mwesigwa R, et al. Association of aging and survival in a large HIV-infected cohort on antiretroviral therapy. *AIDS.* Mar 13; 2011 25(5):701–705. [PubMed: 21160412]
20. Mutevedzi PC, Lessells RJ, Rodger AJ, Newell ML. Association of age with mortality and virological and immunological response to antiretroviral therapy in rural South African adults. *PLoS one.* 2011; 6(7):e21795. [PubMed: 21747959]
21. Negin J, Cumming RG. HIV infection in older adults in sub-Saharan Africa: extrapolating prevalence from existing data. *Bulletin of the World Health Organization.* Nov 1; 2010 88(11):847–853. [PubMed: 21076566]
22. Negin J, van Lettow M, Semba M, Martiniuk A, Chan A, Cumming RG. Anti-retroviral treatment outcomes among older adults in Zomba district, Malawi. *PLoS one.* 2011; 6(10):e26546. [PubMed: 22031839]
23. Negin J, Wariero J, Cumming RG, Mutuo P, Pronyk PM. High rates of AIDS-related mortality among older adults in rural Kenya. *J Acquir Immune Defic Syndr.* Oct; 2010 55(2):239–244. [PubMed: 20639764]
24. Tuboi SH, Brinkhof MW, Egger M, et al. Discordant responses to potent antiretroviral treatment in previously naive HIV-1-infected adults initiating treatment in resource-constrained countries: the antiretroviral therapy in low-income countries (ART-LINC) collaboration. *J Acquir Immune Defic Syndr.* May 1; 2007 45(1):52–59. [PubMed: 17460471]
25. Nakanjako D, Kiragga A, Ibrahim F, Castelnovo B, Kamya MR, Easterbrook PJ. Sub-optimal CD4 reconstitution despite viral suppression in an urban cohort on antiretroviral therapy (ART) in sub-Saharan Africa: frequency and clinical significance. *AIDS research and therapy.* 2008; 5:23. [PubMed: 18957083]
26. Lawn SD, Myer L, Bekker LG, Wood R. CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa. *BMC Infect Dis.* 2006; 6:59. [PubMed: 16551345]
27. Falster K, Petoumenos K, Chuah J, et al. Poor baseline immune function predicts an incomplete immune response to combination antiretroviral treatment despite sustained viral suppression. *J Acquir Immune Defic Syndr.* Mar 1; 2009 50(3):307–313. [PubMed: 19194311]
28. Schacker TW, Bosch RJ, Bennett K, et al. Measurement of naive CD4 cells reliably predicts potential for immune reconstitution in HIV. *J Acquir Immune Defic Syndr.* May 1; 2010 54(1):59–62. [PubMed: 20182359]
29. Castelnovo B, Kiragga A, Afayo V, et al. Implementation of provider-based electronic medical records and improvement of the quality of data in a large HIV program in Sub-Saharan Africa. *PLoS one.* 2012; 7(12):e51631. [PubMed: 23284728]
30. Ministry of Health Uganda. National Antiretroviral Treatment Guidelines for Adults, Adolescents, and Children. Jun. 2009
31. AIDS Control and Prevention (AIDSCAP) Project of Family Health International. The Status and Trends of the Global HIV/AIDS Pandemic: The Francois-Xavier Bagnoud Center for Public Health and Human Rights Of the Harvard School of Public Health. UNAIDS; Nov 28. 1996 1996
32. World Health Organization. WHO Report 2011: Global Tuberculosis Control. World Health Organisation; 2011.
33. Viard JP, Mocroft A, Chiesi A, et al. Influence of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. *J Infect Dis.* Apr 15; 2001 183(8):1290–1294. [PubMed: 11262215]

34. van Lelyveld SF, Gras L, Kesselring A, et al. Long-term complications in patients with poor immunological recovery despite virological successful HAART in Dutch ATHENA cohort. *AIDS*. Feb 20; 2012 26(4):465–474. [PubMed: 22112603]
35. Tissot O, Viard JP, Rabian C, et al. No evidence for proliferation in the blood CD4+ T-cell pool during HIV-1 infection and triple combination therapy. *AIDS*. May 28; 1998 12(8):879–884. [PubMed: 9631141]
36. Hellerstein M, Hanley MB, Cesar D, et al. Directly measured kinetics of circulating T lymphocytes in normal and HIV-1-infected humans. *Nature medicine*. Jan; 1999 5(1):83–89.
37. Douek DC, McFarland RD, Keiser PH, et al. Changes in thymic function with age and during the treatment of HIV infection. *Nature*. Dec 17; 1998 396(6712):690–695. [PubMed: 9872319]
38. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet*. Mar 11; 2006 367(9513):817–824. [PubMed: 16530575]
39. Castelnovo B, Manabe YC, Kiragga A, Kamya M, Easterbrook P, Kambugu A. Cause-specific mortality and the contribution of immune reconstitution inflammatory syndrome in the first 3 years after antiretroviral therapy initiation in an urban African cohort. *Clin Infect Dis*. Sep 15; 2009 49(6):965–972. [PubMed: 19673615]
40. Mermin J, Were W, Ekwaru JP, et al. Mortality in HIV-infected Ugandan adults receiving antiretroviral treatment and survival of their HIV-uninfected children: a prospective cohort study. *Lancet*. Mar 1; 2008 371(9614):752–759. [PubMed: 18313504]
41. Helleberg M, Kronborg G, Larsen CS, et al. Poor CD4 response despite viral suppression is associated with increased non-AIDS-related mortality among HIV patients and their parents. *AIDS*. Mar 27; 2013 27(6):1021–1026. [PubMed: 23196936]
42. Triant VA, Regan S, Lee H, Sax PE, Meigs JB, Grinspoon SK. Association of immunologic and virologic factors with myocardial infarction rates in a US healthcare system. *J Acquir Immune Defic Syndr*. Dec 15; 2010 55(5):615–619. [PubMed: 20827215]
43. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. *Clin Infect Dis*. Aug 15; 2010 51(4):435–447. [PubMed: 20597691]
44. Prosperi MC, Cozzi-Lepri A, Castagna A, et al. Incidence of malignancies in HIV-infected patients and prognostic role of current CD4 cell count: evidence from a large Italian cohort study. *Clin Infect Dis*. May 1; 2010 50(9):1316–1321. [PubMed: 20297953]
45. Kesselring AM, Gras L, Wit FW, et al. Immune restoration and onset of new AIDS-defining events with combination antiretroviral therapy in HIV type-1-infected immigrants in the Netherlands. *Antiviral therapy*. 2010; 15(6):871–879. [PubMed: 20834099]
46. Wanyama, JFN.; Kiragga, A.; Wandera, B.; Kasibante, D.; Ratanshi, RP.; Castelnovo, B. The Role Of Treatment Buddies In Mediating The Relationship Between HIV Treatment Adherence, Mortality And Time To First Switch Of ART In An Urban Clinic Cohort (No. PB 103).. International Conference on AIDS and STIs in Africa (ICASA); Cape Town, South Africa. 2013;

Figure 1. Kaplan-Meier survival by age category among HIV infected adults who initiated ART between January 1, 2004 and January 3, 2012 at the Adult Infectious Diseases Clinic (AIDC) in the Infectious Diseases Institute (IDI) Kampala, Uganda.

Figure 2.

Plotted predicted CD4 after ART initiation by Age category and years on ART from the multilevel mixed-effects linear regression model to evaluate immunological recovery among adults who initiated ART the Adult Infectious Diseases Clinic (AIDC) at the Infectious Diseases Institute (IDI) Kampala, Uganda between 2004 and 2012. In the model; Age at ART start, sex, baseline CD4, baseline WHO stage, Opportunistic infections at ART start were used to predict CD4 after ART start.

Table 1

Characteristics at ART initiation for 9,806 HIV infected patients who initiated ART between January 1 2004 and January 3 2012 at the Adult Infectious Diseases Clinic (AIDC) in the Infectious Diseases Institute (IDI) Kampala, Uganda.

Characteristic	Overall N=9806 N (%)	<50 years N = 9033 N (%)	50-59 years N =615 N (%)	60 years N=158 N (%)	p-value
Gender					
Female	6,351 (64.8)	5,986(66.3)	304 (49.4)	61(38.6)	<0.001
Male	3,455 (35.2)	3,047 (33.7)	311 (50.6)	97(61.4)	
Marital status					
Married/Cohabiting	4903(50.1)	4570 (50.6)	273 (44.4)	60 (38.0)	<0.001
Separated/Divorced/widowed	4263 (43.5)	3,839 (42.5)	329 (53.5)	95 (60.1)	
Single	640 (6.4)	624 (6.9)	13 (2.1)	3 (1.9)	
¹Baseline CD4 (cells/μJ)					
<100	2827 (42.0)	2659 (42.8)	136(32.3)	32(29.9)	<0.001
100-200	2546 (37.8)	2316 (37.2)	187(44.4)	43(40.2)	
200-350	1079 (16.0)	974 (15.7)	78 (18.5)	27(25.2)	
350-500	176 (2.6)	160 (2.6)	15(3.6)	1(0.9)	
>500	117(1.7)	108 (1.7)	5(1.2)	4(3.7)	
²WHO Clinical stage					
Stage I	448 (4.6)	422 (4.7)	20 (3.2)	6 (3.8)	0.017
Stage II	2,950 (30.1)	2730 (30.2)	173 (28.1)	47 (29.8)	
Stage III	3,847 (39.2)	3501 (38.8)	271 (44.1)	75 (47.5)	
Stage IV	2,524 (25.7)	2349 (26.0)	146 (23.7)	29 (18.4)	
Opportunistic infections					
Tuberculosis	1175 (11.9)	1095 (12.1)	65 (10.7)	15 (9.5)	0.300
Kaposi's sarcoma	281 (2.9)	256 (2.8)	20 (3.3)	5 (3.2)	0.800
³BMI Kg^m-²					
<19	2287 (23.3)	2109 (23.3)	147 (23.9)	31(19.6)	0.020
19-25	4929 (50.3)	4573 (50.6)	273 (45.5)	83 (52.5)	
26-30	1132 (11.5)	1041 (11.5)	74 (12.0)	17 (10.8)	
>30	385 (3.9)	341 (3.8)	36 (5.9)	8 (5.1)	
⁴Baseline Regimen (NNRTI)					
Nevirapine based	5933 (60.5)	5485 (60.7)	356(57.9)	92 (58.2)	0.600
Efavirenz based	3842 (39.2)	3520 (38.9)	257 (41.8)	65 (41.1)	
Triple Nucleosides	8 (0.1)	8 (0.1)	-	-	

Characteristic	Overall	<50 years	50-59 years	60 years	p-value
	N=9806	N = 9033	N =615	N=158	
	N (%)	N (%)	N (%)	N (%)	
⁵ Baseline regimen (NRTI)					
<i>Stavudine</i>	4407 (44.9)	4,058 (44.9)	286 (46.5)	63 (40.0)	0.300
<i>Zidovudine</i>	5029 (51.3)	4651 (51.5)	295 (48.0)	83 (52.5)	0.200

¹ Baseline CD4 missing for 3,445 individuals (33.8%) this proportion was similar across the groups

² WHO-Stage at ART initiation was missing for 18 individuals

³ BMI at ART start missing for 1,073 individuals (10.9%) since these individuals didn't have height measurement at baseline.

⁴ Twenty three individuals didn't have their regimen reported

⁵ 6.8% of participants were started on regimens that had neither Stavudine nor Zidovudine.

Table 2

Characteristics at last follow-up for 9,806 adults who started ART between January 1 2004 and January 3 2012 at the Adult Infectious Diseases Clinic (AIDC) in the Infectious Diseases Institute (IDI) Kampala, Uganda

Characteristic	Overall N=9806 N (%)	<50 years N = 9033 N (%)	50-59 years N =615 N (%)	60 years N=158 N (%)	p-value
Current Regimen					
First line	9141 (93.2)	8413 (93.1)	579 (94.1)	149(94.3)	0.200
Second line	616 (6.3)	578 (6.4)	30 (4.9)	8 (5.1)	
Other	26 (0.3)	22 (0.2)	4 (0.6)	0 (0)	
Protease Inhibitor Use	625 (6.4)	586 (6.5)	31 (5.0)	8(5.1)	0.300
Years on ART, Mean(s.d)	5.4 (1.6)	5.5(1.6)	5.5 (1.6)	5.3 (1.6)	<0.001
No. of ART related Toxicity					
None	5393 (55.0)	5009 (55.5)	299 (48.6)	85 (53.8)	0.004
1	3307 (33.7)	3023 (33.5)	235 (38.2)	49 (31.0)	
2	1106 (11.2)	1001(11.2)	81 (13.2)	24 (15.2)	
Follow up status					
Active	5997 (61.2)	5554 (61.5)	364 (59.2)	79 (50.0)	<0.001
Lost to follow up	1450 (14.8)	1339(14.8)	83 (13.5)	28 (17.7)	
Dead	778 (7.9)	672 (7.4)	75 (12.2)	31 (19.6)	
Transferred out	1581(16.1)	1468 (16.2)	93 (15.1)	20 (12.7)	

Table 3

Univariate and multivariate Weibull regression analysis of risk factors for mortality comparing HIV-infected adults on ART 50 years to those <50 years who initiated therapy between January 1, 2004 and January 3, 2012 at the Adult Infectious Diseases Clinic (AIDC) at the Infectious Diseases Institute (IDI) Kampala, Uganda.

Risk factor	Univariate Analysis				Multivariate Analysis			
	<50 years		50 years		<50 years		50 years	
	¹ HR(95% CI)	p-value	¹ HR(95% CI)	p-value	² AHR(95% CI)	p-value	² AHR(95% CI)	p-value
Sex								
Female	Ref	-	Ref	-	Ref	-	Ref	-
Male	1.6 (1.4, 1.9)	<0.001	1.1 (0.1, 1.6)	0.700	0.9 (0.7,1.1)	0.400	1.0(0.6,1.9)	0.900
BMI Category (Kg/M²)								
>30	Ref	-	Ref	-	Ref	-	Ref	-
25-29.9	0.9 (0.6, 1.6)	0.900	1.0 (0.3, 3.3)	0.900	0.7(0.4, 1.4)	0.400	0.6(0.2,2.3)	0.500
19-24.9	1.7 (1.0, 2.7)	0.900	1.6 (0.6, 4.4)	0.500	1.1 (0.6, 1.9)	0.900	0.8(0.3,2.3)	0.600
<19	7.4 (4.6, 12.0)	<0.001	4.1(1.5, 11.7)	0.007	3.3 (1.8, 6.0)	<0.001	1.7(0.5,5.4)	0.400
Baseline WHO Stage^I								
Stage I	Ref	-	Ref	-	Ref	-	Ref	-
Stage II	1.6 (0.8, 3.4)	0.200	1.2 (0.3, 5.1)	0.800	1.2(0.4, 3.4)	0.700	0.8(0.1,6.0)	0.800
Stage III	3.1 (1.5, 6.3)	0.002	1.5 (0.4, 6.1)	0.600	1.8(0.7,4.9)	0.300	0.8(0.1,6.0)	0.800
Stage IV	7.1 (3.5, 14.3)	<0.001	3.3 (0.8, 13.7)	0.100	3.3 (1.2,9.0)	0.020	1.5(0.2,11.6)	0.700
TB diagnosis								
No	Ref	-	Ref	-	Ref	-	Ref	-
Yes	1.4 (1.2, 1.7)	0.001	0.7 (0.3, 1.4)	0.300	0.9 (0.6, 1.2)	0.400	0.6(0.2,1.9)	0.400
KS Diagnosis								
No	Ref	-	Ref	-	Ref	-	Ref	-
Yes	2.7 (2.0, 3.7)	<0.001	1.9 (0.8,4.3)	0.100	1.4(0.9,2.2)	0.100	1.6(0.5,5.5)	0.400
Baseline CD4 Category (cells/mm³)								
>350	Ref	-	Ref	-	Ref	-	Ref	-
101-350	1.9 (0.8, 4.3)	0.100	1.6 (0.4, 6.6)	0.500	2.1 (0.9, 4.9)	0.080	1.4(0.2, 11.0)	0.700
<100	3.4 (1.5, 7.6)	0.003	1.6 (0.4, 6.7)	0.500	2.8 (1.2,6.5)	0.020	1.4(0.2 ,12.0)	0.800
CD4 < 100 cells/mm³ after 1 year on ART								
No	Ref	-	Ref	-	Ref	-	Ref	-
Yes	3.1 (2.5, 3.7)	<0.001	2.8 (1.7, 4.6)	<0.001	2.6 (1.9,3.5)	<0.001	2.7 (1.2, 6.0)	0.020
CD4 < Baseline after 1 year on ART								

Risk factor	Univariate Analysis				Multivariate Analysis			
	<50 years		50 years		<50 years		50 years	
	¹ HR(95% CI)	p-value	¹ HR(95% CI)	p-value	² AHR(95% CI)	p-value	² AHR(95% CI)	p-value
<i>No</i>	Ref	-	Ref	-	Ref	-	Ref	-
<i>Yes</i>	2.3 (1.8, 2.8)	<0.001	3.1 (2.0, 4.8)	<0.001	3.3 (2.5,4.5)	<0.001	5.0 (2.4, 10.3)	<0.001

¹**HR**- Hazard Ratio

²**AHR**-Adjusted Hazard Ratio. (Adjusted for; Sex, BMI, baseline CD4, KS at ART start, TB at ART start, Baseline WHO stage, CD4 <100 after 1 year on ART, CD4 < baseline after 1 year on ART).