The prognostic value of baseline CD4 cell count beyond 6 months of antiretroviral therapy in HIV positive patients in Uganda

Objective: The risk of death is highest in the first few months after initiation of ART. We examined whether initial CD4 count maintains a strong prognostic value among patients with at least 6 months follow-up after the initiation of antiretroviral therapy (ART).

Design: Observational study of HIV patients in Uganda aged 14 years or older enrolled in 10 clinics across Uganda.

Methods: Baseline CD4 cell count of patients with >6 months of follow up were stratified into categories (<50, 50-99, 100-149, 150-249, ≥250 cells/μL). A Kaplan-Meier survival analysis and Cox proportional hazards regression was used to model the associations between baseline CD4 cell count and mortality.

Results: Of 22,315 patients, 20,730 (92.8%) patients had more than 6 months of follow-up. Six hundred and eleven (2.9%) patients died during follow up and 737 (3.6%) of patients were lost to follow-up. Relative to a baseline CD4 cell counts of <50 cells/μL, the adjusted hazard ratios for death were 0.83 (95% confidence interval [CI], 0.67-1.02), 0.71 (95% CI, 0.57-0.88), 0.52 (95% CI, 0.42-0.64), and 0.55 (95% CI, 0.42-0.70) favouring those with baseline CD4 cell counts of 50-99, 100-149, 150-249, and ≥ 250 cells/μL, respectively. Differing ages and male gender increased the likelihood of mortality.

Conclusion: Among patients with >6 months of follow-up on ART, baseline CD4 cell count at initiation was still be of important prognostic value. This suggests that active engagement and earlier treatment initiation is important for long-term survival.
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The prognostic value of baseline CD4 cell count beyond 6 months of antiretroviral therapy in HIV positive patients in Uganda

Edward J Mills¹, Celestin Bakanda², Josephine Birungi², Sanni Yaya¹, Nathan Ford³, for the TASO-CAN Writing Group*

1) Faculty of Health Sciences, University of Ottawa, Ottawa, Canada,
2) The AIDS Support Organization (TASO), Headquarters, Kampala, Uganda
3) Medecins Sans Frontiers, Geneva, Switzerland
* Listed in acknowledgement section.

Correspondence to Edward J. Mills, MSc, PhD, LLM, Faculty of Health Sciences, University of Ottawa, Ottawa, Ontario, Canada; edward.mills@uottawa.ca

Word Count: 1,667

Tables: 1; Figures: 1; Web-appendix 1

Keywords: Mortality, CD4, HIV, antiretroviral therapy, sub-Saharan Africa, Uganda
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**Keywords:** antiretroviral therapy, ART, CD4, HIV, prognosis, sub-Saharan Africa, Uganda
Introduction

CD4 count is a strong prognostic indicator of mortality among individuals infected with HIV in Africa,1-3 and treatment initiation decisions are based on CD4 status.4 In 2010, the World Health Organization (WHO) issued guidance to resource-constrained settings to expand the eligibility of the treated population by recommending initiation of ART when a patient’s CD4 T-cell count reached 350 cells/μL or less, or clinically necessitated,5 but in practice many patients continue to start treatment at much lower CD4 counts. The average CD4 cell count among patients initiating ART in sub-Saharan Africa multi-country studies is between 100 and 130 cells/μL.6

The majority of death among patients who begin ART occurs in the first three months of therapy.7 Patients who survive this initial period are typically considered to have a better likelihood of long-term survival.8,9 Although CD4 counts are increasingly used for determining ART eligibility in many global settings, CD4 counts are costly and are rarely done for clinical follow-up in resource-limited settings. Our study aims to examine whether initial CD4 cell count maintains a strong prognostic value beyond 6 months of ART in a large observational cohort in sub-Saharan Africa.
Methods

Setting
Our study used data collected by The AIDS Support Organization (TASO). TASO was founded in 1987, and has since provided care to over 200,000 patients in Uganda, providing counselling, free access to ART, and regular health care for treatment of opportunistic infections, while actively attempting to retain patients and avoid loss to follow-up. It began free distribution of antiretrovirals in 2004, and currently services 24,000 patients at 11 sites throughout Uganda. We have previously reported on clinical outcomes within this cohort.\textsuperscript{10-13} The TASO cohort is one of the largest cohorts in Africa and is generalizable to many resource-limited settings as it receives funding primarily from the United States Presidents Emergency Plan for AIDS Relief (via CDC) and clinical practice is guided by clinical monitoring rather than regular CD4+ cell counts or any virological monitoring.

Cohort characteristics
The cohort for this analysis involved patients initiated since 2004 and receiving treatment for a minimum duration of 6 months. All included patients are >14 years of age, initiated between January 1, 2000 and February 1, 2010 were included in this study. These patients were followed until either until the time of death or the end of the study period (February 1, 2010). For each patient, we recorded age at the start of antiretroviral therapy (years), gender, baseline CD4 cell count, WHO clinical disease stage, loss to follow-up (defined as a 3-month untraceable absence from a clinic), year antiretroviral therapy started, date last seen for care, and where
applicable, date of death. Patient adherence to ART was defined as ≥95% or <95% and determined by a composite of pharmacy refill records, 3-day self-report, and drug possession ratio. The cohort profile has been previously published. 10

Analysis

CD4 cell counts were stratified into the following categories <50, 50-99, 100-149, 150-249, 250+ cells/μL and patients’ survival estimates were assessed according to baseline CD4 cell counts. Survival probabilities based on baseline CD4 cell count were estimated using a Kaplan-Meier plot using the 6 month period post-initiation as the starting date and compared using the log-rank test. Patients lost to follow-up were censored at the date they were last seen. Patients alive at the date when the study ended were censored at that particular date at which the study was concluded. A weighted analysis was applied, whereby 30% of patients lost to follow-up were assumed dead, weighted by baseline CD4, age and male gender, consistent with published data and modelling studies.14, 15 Unadjusted and adjusted Cox proportional hazards regression were conducted in order to quantify the impact of initial CD4 cell count on the probability of survival after 6 months of treatment, adjusting for three covariates selected a priori: age, gender, and WHO clinical disease stage.16 Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals. To account for missing baseline CD4 cell counts, we also conducted analyses using the multiple imputation method.17 All significance tests were two-sided with a p-value of <0.05. All analyses were conducted using SAS version 8 (SAS Institute, Cary, NC).
Institutional Review

Approval to conduct this study was received from the administrative headquarters ethics board of TASO Uganda, and the Research Ethics Boards of the University of Ottawa and the University of British Columbia in Canada.
Results

Patient Demographics

Of the 22,315 patients ≥ 14 years of age in the TASO program between 2000 and 2010, 20,730 (92.8%) patients had 6+ months of follow-up and were thus included in this study. Baseline characteristics are summarized in web-appendix 1. Patients were followed for a median period of 33 months (Interquartile range, IQR, 31-45 months) and the majority, 70.2%, were female. The median patient age was 37 years (IQR, 31-43 years) and the median CD4 cell count was 146 cells/μL (IQR, 75-208) with 71.6% of patients having CD4 cell counts below 200 cells/μL at the initiation of treatment. Most patients were classified into WHO disease stage II, (55.8%) or III (33.5%). Eighty-five percent of patients maintained ≥ 95% adherence.

Mortality

The majority of deaths (59%) occurred in the first 6 months. Of patients with >6 months of follow up, 611 (2.9%) of patients died and 737 (3.6%) patients were lost to follow-up. Figure 1 shows a Kaplan-Meier graph that projects the survival of patients on ART with 6+ months of follow up, with different baseline CD4 cell count ranges. Higher baseline CD4 counts was consistently associated with probability of survival in the long-term. For patients starting treatment with low CD4 counts (<150 cells/μL), these strata continue to be at a higher risk of mortality, after accounting for 6 months of treatment. Those at greatest risk continued to be those who initiated ART with the lowest CD4 cell counts (< 50 cells/μL).
Table 1 displays the unadjusted and adjusted Cox proportional hazard models for patients with 6 or more months of follow up. The adjusted model indicates that, relative to the lowest CD4 strata, baseline CD4 cell count increases in patients with >6 months of treatment, after adjusting for gender, advanced WHO disease stage, and year of ART initiation. Male gender is an important predictor of mortality.
Discussion

The high risk of early mortality among patients presenting with low CD4 counts is well established, and trials are planned to assess interventions to reduce early mortality among patients with low CD4 counts.\textsuperscript{18} Our study demonstrates that, even after surviving the most difficult first few months of treatment, baseline CD4 count remains a strong prognostic factor of future mortality. Patients starting ART with a lower baseline CD4 count continue to be at significantly higher risk of mortality than those with higher CD4 counts. Earlier recruitment into care through active case finding and earlier initiation of treatment may have important long term benefits.

Our study has low rates of death despite a poorly resourced environment. Strengths of ART delivery in this setting include its community-based approach and directed efforts at improving retention and adherence. It is possible that our findings would differ in cohorts with larger attrition and poor adherence support. We did not CD4 cell count changes between baseline and the 6-month point to assess their prognostic value. However, our goal was to examine patients who had survived and were followed beyond the 6-month period and our assessment of vital status is reliable, as reported elsewhere.\textsuperscript{10-13, 19-21} In a previous analysis, we found that about 26\% of eligible patients at baseline will not initiate ART and are lost to follow up prior to initiation, a third of whom were dead.\textsuperscript{15} We aimed to reduce any bias associated with lost patients by applying a sensitivity analysis that assumes that 30\% of those patients were deceased, based on findings from our previous tracking
study and a similar analysis at a relevant local Ugandan setting, a method we and others have used previously.\textsuperscript{14, 15, 20}

Although our hazard ratios were adjusted to account for other factors such as patient age and gender, these factors are also important variables affecting mortality of HIV patients undergoing ART in Uganda. In this study, men were 40% more likely to die during the greater than 6 month follow-up period. Men are inconsistently represented in treatment programmes in Africa, evident in the significant gender disparity in our patient distribution.\textsuperscript{22} Fewer men begin treatment, and many are initiated at lower CD4 cell counts, and thus generally fare worse than their female counterparts.\textsuperscript{12, 13} These factors were associated with the higher risk of mortality after 6 months of treatment in male patients that was found in our data. We also have found a higher rate of mortality among young people and older adults. Both groups are underrepresented in African cohorts and their higher death rates are largely attributable to the fact that they have historically had poor access to ART and many adolescent patients were likely infected at birth.\textsuperscript{13, 21}

The findings of the study have important prognostic implications for HIV treatment in sub-Saharan Africa. Our results indicate that nadir CD4 cell counts maintain their predictive value of death, even after 6 months of ART treatment. Uganda has recently changed it target CD4 for initiation to <350 cells/μL, yet many African countries have low thresholds.\textsuperscript{23} However, Uganda and many other resource-limited settings have important challenges in even meeting this threshold and more effort needs to go into diagnosing and linking patients into care and treatment programs.
earlier.\textsuperscript{24} The added benefits of earlier initiation include the reduced sexual transmission of the virus,\textsuperscript{25} and increased life expectancy,\textsuperscript{20} a finding that may indicate treatment of infected patients is ultimately cost-saving.\textsuperscript{26}

In conclusion, our study demonstrates that, in Uganda, baseline CD4 count prior to initiation of ART remains a strong prognostic factor even after 6 months of treatment. Early recruitment into care and early initiation of ART remains the best approach to decreasing mortality associated with HIV. Special attention should be devoted to ensuring equitable access to care among more vulnerable including men, adolescents and the elderly.

\textbf{Acknowledgements}

The Canadian Institutes of Health Research (CIHR) funded this study.

\textbf{Conflicts of interest}: None declared.

Author contributions:

Study concept: SB, JG, AH, AK, TR, ES, AS, MS, SY, CB, JB, NF, EM

Data acquisition: CB, JB, NF, EM

Analysis: SB, JG, AH, AK, TR, ES, AS, MS, SY, CC, RL, NF, EM

Drafting manuscript: All

Approval of final manuscript: All
Acknowledgements: TASO-CAN additional writing group: Sarah Bray¹, Jillian Gedeon¹, Ahsan Hadi¹, Ahmed Kotb¹, Tarun Rahman¹, Elaha Sarwar¹, Anna Savelyeva¹, Marika Sévigny¹, Curtis L Cooper², Richard Lester.³

1) Faculty of Health Sciences, University of Ottawa, Ottawa, Canada,
2) Division of Infectious Diseases, Ottawa Hospital, University of Ottawa, Canada,
3) Department of Medicine, University of British Columbia, Vancouver, Canada.


Table 1. Unadjusted and adjusted Cox proportional hazard models of patients with 6+ months follow up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>p-value</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14-19</td>
<td>0.92 (0.54-1.57)</td>
<td>0.758</td>
<td>0.97 (0.57-1.67)</td>
<td>0.919</td>
</tr>
<tr>
<td>20-29</td>
<td>0.60 (0.47-0.78)</td>
<td>&lt;0.001</td>
<td>0.67 (0.52-0.87)</td>
<td>0.003</td>
</tr>
<tr>
<td>30-39</td>
<td>0.67 (0.55-0.83)</td>
<td>&lt;0.001</td>
<td>0.67 (0.55-0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40-49</td>
<td>0.72 (0.58-0.89)</td>
<td>0.002</td>
<td>0.69 (0.55-0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>50+</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Male Gender</td>
<td>1.40 (1.22-1.61)</td>
<td>&lt;0.001</td>
<td>1.40 (1.21-1.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 at ART initiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.84 (0.68-1.04)</td>
<td>0.108</td>
<td>0.83 (0.67-1.02)</td>
<td>0.080</td>
</tr>
<tr>
<td>50-99</td>
<td>0.68 (0.55-0.85)</td>
<td>&lt;0.001</td>
<td>0.71 (0.57-0.88)</td>
<td>0.002</td>
</tr>
<tr>
<td>100-149</td>
<td>0.47 (0.38-0.57)</td>
<td>&lt;0.001</td>
<td>0.52 (0.42-0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>150-249</td>
<td>0.45 (0.35-0.58)</td>
<td>&lt;0.001</td>
<td>0.55 (0.42-0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>250+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO at ART initiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>0.82 (0.52-1.28)</td>
<td>0.369</td>
<td>0.97 (0.62-1.52)</td>
<td>0.898</td>
</tr>
<tr>
<td>Stage 2</td>
<td>1.37 (0.92-2.04)</td>
<td>0.120</td>
<td>1.39 (0.94-2.06)</td>
<td>0.102</td>
</tr>
<tr>
<td>Stage 3</td>
<td>1.79 (1.10-2.91)</td>
<td>0.020</td>
<td>2.03 (1.25-3.28)</td>
<td>0.005</td>
</tr>
<tr>
<td>Year on ART</td>
<td>0.61 (0.58-0.65)</td>
<td>&lt;0.001</td>
<td>0.62 (0.58-0.66)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure 1. Kaplan-Meier probability plot of mortality for patients beginning 6 months after initiation of ART.
### Web-appendix 1. Characteristics of included patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Category</th>
<th>Total</th>
<th>&lt;6 months n (%)</th>
<th>6+ months n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>14-19</td>
<td>333</td>
<td>23(1.5)</td>
<td>310(1.5)</td>
</tr>
<tr>
<td></td>
<td>20-29</td>
<td>3486</td>
<td>315(19.9)</td>
<td>3171(15.3)</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
<td>9774</td>
<td>692(43.7)</td>
<td>9082(43.8)</td>
</tr>
<tr>
<td></td>
<td>40-49</td>
<td>6292</td>
<td>372(23.5)</td>
<td>5920(28.6)</td>
</tr>
<tr>
<td></td>
<td>50+</td>
<td>2430</td>
<td>183(11.5)</td>
<td>2247(10.8)</td>
</tr>
<tr>
<td><strong>Total (n)</strong></td>
<td></td>
<td>2231</td>
<td>1585</td>
<td>20730</td>
</tr>
</tbody>
</table>

| **Gender**                             | Female   | 1549  | 940(59.3)       | 14552(70.2)     |
|                                        | 2        |       |                 |                 |
|                                        | Male     | 6823  | 645(40.7)       | 6178(29.8)      |
| **Total (n)**                          |          | 2231  | 1585            | 20730           |

| **CD4**                                | 0-49     | 3452  | 515(40.6)       | 2937(17)        |
|                                        | 050-99   | 2942  | 211(16.6)       | 2731(15.9)      |
|                                        | 100-149  | 3410  | 181(14.3)       | 3229(18.7)      |
|                                        | 150-249  | 5740  | 249(19.6)       | 5491(31.9)      |
|                                        | 250+     | 2954  | 112(8.8)        | 2842(16.5)      |
| **Total (n)**                          |          | 1849  | 1268            | 17230           |

<p>| <strong>WHO Stage at ART initiation</strong>        | Stage 1  | 465   | 15(1.5)         | 450(3.3)        |
|                                        | Stage 2  | 7985  | 375(36.7)       | 7610(55.8)      |
|                                        | Stage 3  | 4982  | 419(41)         | 4563(33.5)      |
|                                        | Stage 4  | 1220  | 214(20.9)       | 1006(7.4)       |</p>
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Category</th>
<th>Total (n)</th>
<th>&lt;6 months n (%)</th>
<th>6+ months n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td></td>
<td>1465</td>
<td>1023</td>
<td>13629</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
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<tr>
<td></td>
<td></td>
<td>1023</td>
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<tr>
<td></td>
<td></td>
<td>13629</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>Yes</td>
<td>1498</td>
<td>887 (3.9)</td>
<td>611 (2.7)</td>
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<tr>
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<td>Total (n)</td>
<td>2231</td>
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<td>20730</td>
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<td></td>
<td></td>
<td>20730</td>
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<tr>
<td>Lost to Follow-up</td>
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<td>2088</td>
<td>889(56.1)</td>
<td>19993(96.4)</td>
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<td></td>
<td>Total (n)</td>
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<td>1585</td>
<td>20730</td>
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Manuscript reference number: AIDS-D-12-00168

Dear Editors:

I hope you are well. Thank you very much for the detailed reviews received from the reviewers on our submitted manuscript. We are grateful to the reviewers for the effort and expertise that they contributed towards improving this manuscript. Below, we provide responses to the reviewers suggestions. Our responses are marked with bullets.

Editor's Comments: Please justify the number of authors and specifically why there are 12 authors from Canada (see comment of reviewer 4)

- Thank you for this comment. We always promote the authorship of our junior colleagues and, in particular, our Ugandan colleagues. We have a larger number of Canadian authors on this manuscript as it originated out of a graduate class project and a publication to these junior colleagues means far more than to our senior authors, including our Ugandan authors. Therefore, the first 8 authors are graduate students. These are the authors who conceptualized the study, ran the analysis, and wrote the initial drafts of the manuscript and fulfill the ICMJE requirements for authorship. We have now changed this to a group authorship “The TASO-CAN Collaboration” as that is the name of the funded collaboration between the Canadian investigators and TASO in Uganda. We now have 5 listed authors and 10 acknowledged individuals.

Reviewer #1:
Strengths and weaknesses.
1) A large well-characterized observational cohort is used.
   - Thank you. No changes requested.
2) Competent statistical analysis which enabled quantification of the impact of initial CD4 T-cell count on the probability of survival after at least 6 months of ART.
   - No changes requested.
3) The data is neither very novel nor unexpected, but does reiterate clearly that early treatment initiation is important for long-term survival (e.g. after 6+ months of
treatment) particularly in patients with initial CD4 T-cell counts of <150.

- Thank you. No changes requested.


- Thank you. We believe that this current manuscript adds context that the long term complications are directly related to when a patient initiates.

5) It is interesting that men, adolescents and the elderly appear to be more vulnerable than women - men being 40% more likely to die in the >6month follow-up period. Clearly work needs to be done to persuade these vulnerable groups to begin treatment earlier.

- Thank you. We agree and hope this manuscript will highlight this to a wider audience.

6) The discussion makes an excellent case for scaling up investments in ART in the developing world.

- Thank you. No changes requested.

Reviewer #2: N/A

Reviewer #3: N/A

Reviewer #4:
1) The study describes the that long term mortality in a very large, well controlled HIV infected Ugandan cohort after induction of HAART is dependent on base line CD4 counts. This relationship is convincing. However the important, overall, very impressive low mortality rate is not really emphasized. The differences become significant partly due to the unusually large sample size and good long term follow-up, 20730, which is unique to this study. It is however likely that the effects should be more pronounced in cohorts with less than the 85% with >95% adherence reported here.

- Thank you. We agree and have added the following text to the discussion.
  “Our study has low rates of death despite the poorly resourced environment. Strengths of ART delivery in this setting include its community based approach and directed efforts at improving retention and adherence. It is possible that our findings would differ in cohorts with larger attrition and poor adherence support.”

2) It is implicit that the baseline CD4 is that at the start of treatment; however from the methodology it appears that it is really at recruitment. Since the date of treatment start is available any difference between date of CD4 count and treatment should be commented on.

- Thank you. We agree with this excellent point. We have now added the following text: Abstract “This suggests that active engagement and earlier treatment initiation is important for long-term survival.”
  o Page 9. “Earlier recruitment into care through active case finding and earlier initiation of treatment may have important long term benefits.”
Page 11 “Early recruitment into care and early initiation of ART remains the best approach to decreasing mortality associated with HIV.”

3) As the authors point out the majority of deaths (59%) occur within the first 6 months, this could well be illustrated as part of fig 1. (0-6 months) using ITT data for the whole cohort in this interval. This would make more evident that only part of the y-axis is shown to emphasize the point of the argument (the 80-100% interval).
   - Thank you for this comment. We examined this in sample graphs. However, because the majority of death occurs in this time period, it is very difficult to discern from the graphs the different CD4 strata and would be unclear for readers. We leave this up to the editor to suggest.

4) In the Web-appendix 1 it is questionable what the X2 p-values mean when used in the tables larger than 2x2 (i.e. age). If the authors want to make a point on the distribution it should be more explicitly analyzed. (also % are lacking for death).
   - Thank you for this comment. We have removed the p-values and added the percentage of deaths.

5) The MS is laudably brief and concise. It is however disturbing that 12 of the authors are from Canada (and one designated '4’ unaccounted for) and only 2 from Uganda representing the impressive organizational, clinical and laboratory team who collected the data. This is true in spite of the earlier publications, ref 10-13, with more prominent Ugandan authorships.
   - Thank you for this comment. We agree that authorship is an important issue and we always encourage and promote our Ugandan colleagues. In this case, we are also encouraging and promoting our most junior of colleagues who conceptualized the study, ran the analysis and wrote the initial drafts of the manuscript. We have now changed the authorship to a group authorship “The TASO-CAN Collaboration.”
   - We have now corrected the omission of Nathan Ford, a collaborator (4) from Medecins Sans Frontiers.

6) In the Introduction a sentence ‘Patients who?’ is duplicated. The comment below on lack of CD4 counts at follow-up is illogical given the context.
   - Thank you. We have corrected this.

Reviewer #5:
1) This in an observational study of HIV patients in Uganda aged 14 years or older enrolled in 10 clinics across Uganda for which The AIDS Support Organization (TASO) has collected data. The TASO cohort is one of the largest cohorts in Africa. The objective of the study is to confirm that initial CD4 count maintains a strong prognostic value among patients with at least 6

- Thank you. No change requested.

2) The study has some limits recognised by the Authors: CD4 cell count changes between baseline and the 6-month point to assess their prognostic value is not reported. However, the study has some important prognostic implications for HIV treatment in sub-Saharan Africa, confirming that HIV patients starting ART with a lower baseline CD4 count continue to be at significantly higher risk of mortality than those with higher CD4 counts. Minor revision on the text are required, may be better reduced to "letter"

- Thank you for these comments. We have made some revisions on the text to reduce the word count.

We greatly appreciate the time and expertise of the reviewers and we hope you will agree the manuscript is importantly improved.

Sincerely

Edward Mills
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