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# BMJ Open

**Body mass index, proteinuria and total lymphocyte counts  
in predicting treatment responses among HIV-infected  
individuals initiated on antiretroviral treatment in Dar es  
Salaam, Tanzania, 2019: a cohort study**

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3 **1 Body mass index, proteinuria and total lymphocyte counts in predicting treatment**  
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5 **2 responses among HIV-infected individuals initiated on antiretroviral treatment in Dar es**  
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7 **3 Salaam, Tanzania, 2019: a cohort study**  
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19 **Keywords:** monitoring ART treatment; HIV/AIDS; CD4 count; BMI in HIV; proteinuria in  
20 HIV; viral suppression

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3 22 **Abstract**  
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6 23 **Objectives:** To explore the potential use of body mass index, proteinuria, and total lymphocyte  
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8 24 count changes in predicting immunological and virological response in HIV-infected individuals  
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10 25 initiated on antiretroviral therapy (ART).  
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14 26 **Design:** Prospective cohort study.  
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17 27 **Setting:** Three urban HIV care and treatment centres (CTC) in Dar es Salaam.  
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20 28 **Participants:** HIV-infected individuals initiating ART.  
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23 29 **Outcome measures:** HIV viral load <1000 copies/ml (virally suppressed) at six months after  
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25 30 ART initiation.  
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28 31 **Results:** Of 215 (out of 220 enrolled) participants who returned for evaluation at six months, 147  
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30 32 (66.8%) were female. At six months of follow-up, 89.4% (76/85) of participants with sustained  
31  
32 33 weight gain were virally suppressed compared to 31.8% (7/22) with sustained loss,  $p < 0.001$ . In  
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34 34 participants who were lymphopaenic at baseline, an increase to normal total lymphocyte counts at  
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36 35 six months was associated with an increase in CD4 count compared to participants who remained  
37  
38 36 lymphopaenic, 96.2% (50/52) vs. 54.8% (17/31),  $p < 0.001$ . At baseline, 50.0% (110/220) had  
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40 37 proteinuria. In participants without proteinuria from baseline to six months, 89.8% (79/88) were  
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42 38 virally suppressed compared to participants with proteinuria at baseline and/or three months,  
43  
44 39 85.6% (77/90), those with persistent proteinuria, 30.8% (8/26), and proteinuria at six months only,  
45  
46 40 45.5% (5/11),  $p < 0.001$ . In modified Poisson regression, the independent predictors other than CD4  
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48 41 cell counts for viral non-suppression at six months among HIV-infected individuals initiating on  
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50 42 ART were BMI loss >5% from baseline to six months, {adjusted RR 2.73, 95% CI (1.36-5.47)},  
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3 43 lymphopaenia at six months, {adjusted RR = 4.54, 95% CI (2.19-9.39)}, and proteinuria at six  
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5 44 months {adjusted RR = 2.63, 95% CI (1.25-5.54)}.

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8 45 **Conclusions:** Changes in body mass index, total lymphocyte count, and presence of proteinuria  
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10 46 can monitor and predict ART response and may be particularly helpful in settings when CD4  
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13 47 counts and viral load monitoring are unavailable.

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3 **49 Article Summary**  
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6 **50 Strengths and limitations of this study**  
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9 **51** ➤ We had complete data on 98% of the originally enrolled participants.  
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11 **52** ➤ In resource-constrained situations, when viral load and CD4 testing are not easily available,  
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13 models such as ours with locally determined easily computable prediction cut-offs can be  
14 **53**  
15 utilized by clinicians to make clinical decisions.  
16 **54**  
17 **55** ➤ Our findings require validation in a study with larger sample size.  
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19 **56** ➤ Local (and time-varying) conditions and treatment standards may influence some of the  
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21 patterns we observed, both in prevalence and in effect.  
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## 59 Introduction

60 In 2019 about 38 million people were living with HIV globally, with 1.7 million in Tanzania  
61 accounting for an estimated prevalence of 4.8% in the Tanzanian population aged 15-49 years (1).  
62 Viral load testing is the recommended method for monitoring HIV treatment response (2).  
63 However, viral load testing in resource-constrained settings is challenged by limited access, high  
64 costs, unavailability at district levels, and in areas where available, a shortage of reagents,  
65 compounded by challenges with equipment maintenance (3), as happened during the COVID-19  
66 pandemic.

67 There is no doubt that viral load testing is effective in monitoring patient treatment adherence and  
68 HIV resistance. However, in resource-constrained areas that may not always be able to perform  
69 viral load testing, there is a need for readily available and routinely assessed objective measures  
70 that may predict early viral non-suppression or measures that may help with interim evaluation of  
71 patients suspected to have treatment failure who will thereafter need additional follow up with  
72 viral load testing. HIV-infected patients are routinely assessed for weight, height, renal function,  
73 and complete blood counts before initiation of combined antiretroviral treatment (ART). These  
74 assessments are repeated at intervals of three months, six months and biannually after ART  
75 initiation. Adverse changes in such parameters from baseline or subsequently at follow-up visits  
76 provides useful information about treatment responses and may identify a targeted group of  
77 patients to be prioritized for viral load testing before a decision to switch the ART regimen.

78 Routine parameters such as body mass index, total lymphocyte counts, and protein in urine are  
79 easily available and can be evaluated in combination for HIV treatment monitoring. Weight loss  
80 is one of the major manifestations of advanced HIV infection. Factors hypothesized to contribute

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3 81 to weight loss include; metabolic alterations, anorexia, malabsorptive disorders, hypogonadism,  
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5 82 and excessive cytokine production (4)  
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8 83 Weight gain following ART initiation may reflect slowed resting energy expenditure resulting  
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10 84 from viral suppression and a decrease in HIV enteropathy (5). Weight gain, especially among  
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12 85 individuals with low BMI, is associated with improved survival and decreased risk of clinical  
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14 86 failure (6). ART responses depend on adherence (7), nutritional status at baseline (8), HIV subtype  
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16 87 (9), and ART combination regimen (10). In Port Harcourt, Nigeria, among 318 participants with  
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18 88 HIV infection aged  $\geq 18$  years initiated on ART, almost 70% and 55% of participants gained at  
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20 89 least 1 kg weight in the first six months and one year of treatment, respectively (11). Previous  
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22 90 studies in Tanzania have shown that a decrease in nutrition status within the first three months of  
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24 91 ART initiation was associated with mortality (12).  
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30 92 HIV-associated nephropathy (HIVAN) is the most common renal biopsy finding in HIV-infected  
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32 93 patients with a prevalence ranging from 4.7 to 38% (13). Proteinuria and elevated creatinine have  
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34 94 been associated with AIDS-defining illness and death (14). Urine assessment for protein by  
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36 95 dipstick can detect renal disease and progression, especially as renal biopsy, an invasive procedure,  
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38 96 is not readily available in most resource-constrained settings.  
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42 97 HIV is associated with progressive destruction of CD4+ T-helper lymphocytes responsible for the  
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44 98 profound immunodeficiency that underlies AIDS (15). As CD4 cells are a subset of lymphocytes,  
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46 99 any significant change in CD4 cells will cause a parallel change in total lymphocyte counts (16).  
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49 100 This study aimed at assessing the following routinely accessible parameters: body mass index,  
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51 101 proteinuria, and total lymphocyte counts (TLC), and their patterns of change in monitoring HIV  
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53 102 treatment responses at six months following ART initiation.  
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## 103 **Methods**

### 104 **Study design and population**

105 This cohort study was conducted in three urban care and treatment centres (CTC) in Temeke  
106 district, Dar es Salaam: Temeke regional referral hospital, Mbagala Rangi-tatu district hospital,  
107 and Mbagala Kizuiani dispensary between September 2018 to April 2019. The centres were chosen  
108 due to large numbers of ART naïve clients, amounting to 60 or more per clinic per month. The  
109 sites have an organized CTC and follow up plan for clients. Participants were initiated on ART  
110 based on the Tanzanian National guidelines (17) with a default regimen of tenofovir, lamivudine  
111 and efavirenz unless contraindicated.

### 112 **Sample size estimation**

113 To determine the minimum detectable relative risks with the power of 80% in univariate analysis  
114 for this observational study for which the sample size was determined by practical considerations,  
115 we used total number of cases between 40 and 50 and group numbers (rounded to 5) similar to the  
116 exposed groups: 115 for stable BMI, 20 for decreased BMI, 35 for lymphopaenia and proteinuria  
117 at 6 months, 80 for age over 40, 145 for female sex, 45 for secondary education or higher, 100 for  
118 employment, 115 for never married, 80 for stage greater than 1. In all cases but BMI, the size of  
119 the reference group was considered to be 215 - the number in the exposed group, except that 80  
120 (gain) was used for the pairwise comparisons of BMI change. The minimum detectable risk ratios  
121 were 3.77, 2.56, 2.94, 2.94, 2.74, 2.59 (or <0.12), 2.47, and 2.44, respectively.

### 122 **Data collection**

123 We used an interviewer-based structured tool to conduct face-to-face interviews to obtain socio-  
124 demographic and baseline characteristics such as age, sex, occupation, the highest level of

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3 125 education attained, marital status, and clinically assessed the participant's WHO HIV clinical  
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5 126 stage. A participant's baseline weight was measured using a SECA weighing scale recording to  
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7 127 the nearest 0.5 kg and height using a wall stadiometer recording to the nearest 0.5 cm. Body mass  
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9 128 index was then computed by dividing the weight in kg by the height in meters squared, the  
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11 129 interpretation of which was adapted from WHO (18).

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15 130 About 10ml of venous blood was collected aseptically from each participant; 5ml for CD4 cell  
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17 131 counts, analysed using BD FACSCount™ (Becton Dickenson, USA) and 5ml for complete blood  
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19 132 count to obtain the total lymphocyte counts, analyzed by an auto-analyzer (Cell DNY1800 from  
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21 133 Abbott Diagnostics Division, USA). TLC was categorized as lymphopaenia ( $<1 \times 10^9/L$ ), normal  
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23 134 lymphocyte ( $1 \times 10^9/L$  to  $4 \times 10^9/L$ ), and lymphocytosis ( $>4.0 \times 10^9/L$ ). We assessed for proteinuria  
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25 135 by collecting about 15ml of a fresh urine sample from each participant into an empty, clean, dry  
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27 136 container and tested using CYBOW™ strips (DFI Co. Ltd, Korea). Proteinuria was categorized as  
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29 137 negative proteinuria (no proteinuria), trace or 1+ proteinuria (equivalent to 30 to 100 mg/dl), 2+  
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31 138 proteinuria (equivalent to 100 to 300 mg/dl), 3+ proteinuria (equivalent to 300 to 1000 mg/dl), and  
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33 139 4+ proteinuria (equivalent to greater than 1000 mg/dl).

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39 140 At three and six months after ART initiation, a repeat assessment of participants was done for CD4  
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41 141 cell counts, TLC, proteinuria, and weight. At six months, an additional 5ml of blood was collected  
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43 142 from each study participant for viral load measurement using the Abbott RealTime HIV-1 assay.  
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45 143 Participants were classified as virally suppressed at six months after ART initiation if their HIV  
46  
47 144 viral load was  $<1000$  copies/ml, according to Tanzania HIV treatment guidelines. Levels and  
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49 145 changes in BMI, lymphocytes, and proteinuria were compared between participants who were HIV  
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51 146 suppressed and that of HIV not suppressed.

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3 147 BMI was considered to have changed between one time point and another if it increased or  
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5 148 decreased by over 5%. BMI changes from ART initiation to six months were categorized into three  
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8 149 groups as (i) loss of more than 5%, (ii) stable (change between -5% and 5%, or (iii) gain of more  
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10 150 than 5%. The TLC were categorized as (i) lymphopaenia  $< 1 \times 10^9$  cells/L, (ii) normal lymphocyte  
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12 151 count  $1-4 \times 10^9$  cells/L (iii) Lymphocytosis  $> 4 \times 10^9$  cells/L. The TLC pattern change was  
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15 152 categorized as (i) lymphopaenic at 6 months, regardless of the status at baseline or three months;  
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17 153 (ii) increased from lymphopaenic to normal or higher; (iii) stayed normal or higher (no  
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19 154 lymphopaenia seen). Urinary protein patterns were categorized as (i) proteinuria at six months  
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22 155 regardless of baseline proteinuria status; (ii) proteinuria at baseline and/or third month but not six  
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24 156 months; and (iii) no proteinuria seen.

### 25 26 27 157 **Patient and public involvement**

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30 158 Patients or members of the public were not involved in the design, or conduct, or reporting, or  
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32 159 dissemination plans of the research.

### 33 34 35 160 **Statistical methods**

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38 161 Data were analysed using IBM® SPSS® Statistics version 26, R, and SAS version 9.4 (Cary, NC).  
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40 162 Categorical variables such as age group, sex, marital status, level of education, occupation,  
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42 163 categories of BMI, CD4 count, proteinuria, TLC, BMI change, TLC change, and proteinuria  
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44 164 change were summarized as frequencies and proportions. Continuous variables such as age, BMI,  
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46 165 and CD4 count were summarized as means and standard deviations. When necessary, small groups  
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48 166 were combined for analysis. To determine the association between BMI, TLC or urine protein to  
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51 167 CD4 count, we used correlation.

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3 168 To determine the relationships between individual predictors and viral non-suppression at six  
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5 169 months, we first used modified Poisson regression for univariable analysis, to determine which  
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7 170 variables to include in the multivariable model. For multivariable prediction, all predictors in the  
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9 171 univariable model with a p-value of  $<0.2$  and age, a known confounder, were entered into the  
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11 172 modified Poisson regression model. The results of the Poisson regression model were presented  
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13 173 as relative risk and 95% confidence interval (RR; 95% CI). To determine the test characteristics  
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15 174 (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)) of a  
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17 175 score based on the multivariable model, we used two cut-off levels, based on the first quartile and  
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19 176 median of the score among the non-suppressed. The score was the sum of the rounded coefficients  
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21 177 for the variables for which the confidence intervals did not include 1 in a model containing only  
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23 178 these variables. Since these all rounded to 1, this is equivalent to simply counting the number of  
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25 179 these characteristics.

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27 180 Based on practices in low resourced clinics, communication with the patient and the decision to  
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29 181 change the ART regimen depends on the patient's virological status at six months. CD4 cell counts  
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31 182 depend on a blood sample collected at the six-month visit and are therefore unavailable for  
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33 183 immediate decision making. We, therefore, excluded all CD4 variables from the model and used  
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35 184 parameters available at the time of the six-month visit to predict viral non-suppression.  
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## Results

186 A total of 220 participants were enrolled in the study over a month, and each participant was  
 187 followed up for six months. Two participants were lost to follow up at three months, two died  
 188 before six months of follow up, and one participant, a long-distance truck driver, was out of the  
 189 country at the time of the 6-month follow up. Therefore, our analysis data set includes the  
 190 remaining 215 participants. Details of enrolment are shown in Fig 1.

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193 **Figure 1. Consort diagram.**

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### 196 **Baseline characteristics of study participants**

197 Of the 215 participants analysed, the mean age (SD) was  $37.1 \pm 11.5$  years, 146 (68%) were female,  
 198 113 (53%) were never married, 45 (21%) had secondary education or higher, and 117 (54%) were  
 199 unemployed (Table 1). Most participants, 59.5%, had normal BMI, while 27% were overweight,  
 200 and 13% were underweight. Most participants, 113 (62%), were in WHO HIV clinical stage I, and  
 201 only eight (4%) were in stage IV, though 93 (43%) had CD4 counts of 350 cells/ml or below; 83  
 202 (39%) were lymphopaenic, and 111 (52%) had proteinuria at baseline.

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204 **Table 1. Baseline characteristics of 215 study participants initiating ART, Dar es Salaam,**  
 205 **Tanzania, 2019.**

Characteristic	n (%)	Mean $\pm$ SD
Age (years)		$37.1 \pm 11.5$
Age group (years)		
18 – 30	69 (32.1%)	

	31 – 40	72 (33.5%)	
	41 – 50	45 (20.9%)	
	>51	29 (13.5%)	
<b>Sex</b>			
	Female	146 (67.9%)	
	Male	69 (32.1 %)	
<b>Level of education</b>			
	No education	10 (4.7%)	
	Primary education	160 (74.4%)	
	Secondary education	42 (19.5%)	
	Higher education	3 (1.4%)	
<b>Employment Status</b>			
	Not employed	117 (54.4%)	
	Employed	98 (45.6%)	
<b>Marital status</b>			
	Ever married	102 (47.4%)	
	Never married	113 (52.6%)	
<b>Body mass index (kg/m<sup>2</sup>)</b>			22.9 ± 4.3
	Underweight	28 (13.0%)	
	Normal weight	128 (59.5%)	
	Overweight/Obese	59 (27.4%)	
<b>WHO HIV clinical stages</b>			
	Stage I	133 (61.9%)	
	Stage II	30 (14.0%)	
	Stage III	44 (20.5%)	
	Stage IV	8 (3.7%)	
<b>CD4 cell counts (cells/mm<sup>3</sup>)</b>			401 ± 253
	<200	55 (25.6%)	
	200-350	38 (17.7%)	
	351-500	39 (18.1%)	
	>500	83 (38.6%)	
<b>Lymphocyte counts (x10<sup>9</sup>cells/L)</b>			1.6 ± 1.2
	<1	83 (38.6%)	
	1-4	126 (58.6%)	
	>4	6 (2.8%)	
<b>Proteinuria</b>			
	No proteinuria	104 (48.4 %)	
	1+ (30 – 100 mg/dl)	80 (37.2%)	
	2+ (100 – 300 mg/dl)	27 (12.6%)	
	3+ (300 – 1000 mg/dl)	4 (1.9%)	



206 CD4: Cluster of differentiation 4; HIV: Human Immunodeficiency Virus; SD: Standard Deviation

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209 **Table 2. Predictors of HIV viral load non-suppression at six months among 215**  
 210 **participants initiating ART, Dar es Salaam, Tanzania, 2019.**

Variable	Total	HIV non-suppression at six months n (%)	RR (95% CI)	Adjusted RR (95% CI)
<b>Age (years)</b>				
< 40	136	26 (19%)	1	1
≥40	79	20 (25%)	1.32 (0.79-2.21)	1.43 (0.91-2.26)
<b>Sex</b>				
Female	146	35 (24%)	1.50 (0.81-2.78)	1.27 (0.73-2.20)
Male	69	11 (16%)	1	1
<b>Level of Education</b>				
Primary or less	170	37 (22%)	1	
Secondary or higher	45	9 (20%)	0.92 (0.48-1.76)	
<b>Employment Status</b>				
Not employed	117	24 (21%)	1	
Employed	98	22 (22%)	1.09 (0.66-1.83)	
<b>Marital status</b>				
Never married	113	19 (17%)	1	1
Ever married	102	27 (26%)	1.57 (0.93-2.66)	1.34 (0.84-2.16)
<b>Body mass index</b>				
<b>Change from baseline to three months</b>				
Loss >5%	28	17 (61%)	4.93 (2.41-10.09)	
Stable	122	21 (17%)	1.40 (0.66-2.99)	
Gain >5 %	65	8 (12%)	1	
<b>Change from baseline to six months</b>				
Loss >5%	20	16 (80%)	7.11 (3.69-13.69)	2.73 (1.36-5.47)
Stable	115	21 (18%)	1.62 (0.78-3.36)	1.87 (0.95-3.68)
Gain >5 %	80	9 (11%)	1	1
<b>HIV clinical stage</b>				
I	133	24 (18%)	1	1
II	30	8 (27%)	1.48 (0.74-2.97)	1.14 (0.63-2.08)
III and IV	52	14 (27%)	1.49 (0.84-2.66)	0.82 (0.51-1.31)
<b>Total lymphocyte count change from baseline to six months</b>				

Ended lymphopaenic	37	27 (73%)	7.66 (4.32-13.60)	4.54 (2.19-9.39)
Lymphopaenic to normal	52	7 (13%)	1.41 (0.59-3.40)	1.59 (0.66-3.80)
Lymphopaenia not seen	126	12 (10%)	1	1
<b>Pattern of change in proteinuria</b>				
Proteinuria at 6 months regardless of baseline proteinuria status	37	24 (65%)	6.73 (3.34-13.58)	2.63 (1.25-5.54)
Proteinuria at baseline and/or 3 months but not 6 months	95	14 (15%)	1.53 (0.67-3.47)	1.26 (0.62-2.57)
No proteinuria seen	83	8 (10%)	1	1

211 CI: confidence interval; RR: relative risk; ART: antiretroviral therapy.

212 Univariable and multivariable analysis by modified Poisson regression.

213

214 BMI and CD4 count were directly correlated at baseline, 3, and 6 months. TLC and CD4 count  
 215 were moderately positively correlated; while urine protein and CD4 count were inversely  
 216 correlated (see Supplementary Figures 1, 2, and 3 in Additional file 1).

217

### 218 **Predictors of viral non-suppression at six months among HIV-infected participants** 219 **initiated on ART**

220 Only 46 participants (21%) were not virally suppressed at six months. The strongest clinical  
 221 predictors of viral non-suppression in the multivariable analysis were lymphopaenia at six months  
 222 irrespective of baseline lymphocyte status, with 73% of participants with lymphopaenia at six  
 223 months not being suppressed. After adjusting for other factors, lymphopaenia at six months was  
 224 associated with HIV non-suppression {RR = 4.54, 95% CI (2.19-9.39)}. Among participants with  
 225 a drop in body mass index at six months of 5% or more from baseline, 80% were non-suppressed  
 226 {RR = 2.73; 95% CI (1.36-5.47)}. The risk of HIV non-suppression at six months was higher

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3 227 among participants with proteinuria at six months {RR = 2.63; 95% CI (1.25-5.54)}, Table 2. The  
4  
5 228 area under the Receiver Operating Characteristic (ROC) curve for the multivariable model was  
6  
7 229 0.895 (Fig 2). Baseline HIV stage was not related to HIV non-suppression at six months, {adjusted  
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9  
10 230 RR = 1.14, 95% CI (0.63-2.08)} for baseline WHO HIV clinical stage II and {adjusted RR = 0.82,  
11  
12 231 95% CI (0.51-1.31)} for advanced baseline WHO HIV clinical stages (III and IV)}.

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14  
15 232 Using the rounded coefficients of the three variables in a model containing only these variables,  
16  
17 233 which all rounded to 1, we made a “prediction score” with values 0 (n=154, of which 10 were non-  
18  
19 234 suppressed), 1 (n=36, 13 non-suppressed), 2 (n=17, 15 non-suppressed), and 3 (n=8, all non-  
20  
21 235 suppressed). The median value of this score among the non-suppressed was 1.5 and the first  
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23 236 quartile value was 1. Thus, having any 2 of the risk factors would be a conservative predictor of  
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26 237 non-suppression, and having any one would be less conservative.

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3 238 **Figure 2. Receiver Operating Characteristic curve assessing a model using BMI decrease,**  
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5 239 **proteinuria, and total lymphocyte counts to predict viral non-suppression among HIV-**  
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7 240 **infected individuals initiated on ART in Dar es Salaam, Tanzania, 2019**  
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17 243 Using the median score among the non-suppressed as a cut-off (equivalent to having any two of  
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19 244 the components), the sensitivity predicting non-suppression was 0.50, and the specificity was 0.99.  
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21 245 Only 12% of the study population met this criterion. When we lowered the cut-off scores to the  
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23 246 first quartile value among the non-suppressed (i.e. any one of the components), the sensitivity was  
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25 247 0.78 and the specificity was 0.85, with 28% of the study population meeting this criterion.  
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## 249 Discussion

250 This cohort study recruited ART naïve HIV-infected individuals from three care and treatment  
251 centres in Dar es Salaam, Tanzania, with the aim of assessing the utility of total lymphocyte count,  
252 body mass index, and proteinuria in predicting ART responses at six months. The intention of this  
253 study is not to replace CD4 cell count testing and HIV viral load monitoring but to assist clinicians  
254 when faced with decision making if these standard monitoring parameters are not easily accessible.  
255 Contrary to earlier studies done when the ART medications were not as effective as the current  
256 ones (12), patient characteristics at ART initiation did not affect the probability of viral non-  
257 suppression at six months, whereas patterns of change and the patient's status at 6 months were  
258 highly predictive.

259 Baseline WHO HIV clinical stage did not help predict HIV non-suppression at six months,  
260 possibly because under the current "Test and Treat" strategy (19), most individuals initiating ART  
261 are in WHO HIV clinical stages I and II (76% of our sample). Current therapy is highly effective  
262 except for a few patients whose disease is so advanced that they die before the medication can  
263 improve their immune status (2 patients in this study). Symptomatic individuals with advanced  
264 HIV will likely adhere to treatment to alleviate their symptoms. Perhaps patients with advanced  
265 disease fear death and therefore are motivated to adhere to ART, with eventual viral suppression.  
266 Advanced HIV disease has been shown to be linked with ART adherence (20). Some studies,  
267 however, indicate that early HIV stages are linked with high ART adherence and viral suppression  
268 (21).

269 Lymphopaenia at six months, a decrease in body mass index of 5% or more from baseline, and  
270 proteinuria predicted HIV non-suppression at six months. Lymphopaenia at six months was the  
271 strongest predictor for HIV non -suppression at six months. Lymphopaenia at six months predicted

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3 272 HIV non-suppression irrespective of a participant's lymphocyte count (normal or low) before ART  
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5 273 initiation. CD4 cells are a subset of lymphocytes and therefore lymphopaenia could be indicative  
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7 274 of a decline in CD4 cells, as a result of high HIV replication with high viral load signifying viral  
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9 275 non-suppression with consequent CD4 cell destruction. Lymphopaenia was significantly  
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11 276 associated with CD4 <500 cells/mm<sup>3</sup> at all time points. In this study, an increase in total  
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13 277 lymphocyte cell count from lymphopaenia to normal lymphocyte counts from baseline to six  
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15 278 months was significantly associated with an increase in CD4 cell count (Additional file 1). Total  
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17 279 lymphocyte count is sensitive and specific in predicting CD4 cell counts (16,23) though there have  
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19 280 been contradictory reports (23). The assessment of total lymphocyte counts among patients on  
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21 281 ART, therefore, could serve as an alternative, especially in settings with limited availability of  
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23 282 CD4 cell count measurement. A drop in total lymphocyte count in such a setting can alert a  
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25 283 clinician to the likelihood of immunological failure.

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27 284 Weight loss with consequent BMI drop of 5% or more at six months while on ART from weight  
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29 285 prior to ART initiation, predicts HIV non-suppression, though HIV non-suppression was not  
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31 286 associated with being underweight prior to ART initiation, perhaps because of the low prevalence  
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33 287 of underweight leading to low power. In this study, sustained weight gain was significantly  
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35 288 associated with viral suppression and sustained weight loss was associated with viral non-  
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37 289 suppression at six months of ART. An increase in weight and hence BMI may be a sign of immune  
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39 290 status improvement signalling a return to health (24) and improved survival (25), while a decrease  
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41 291 in weight and hence BMI may be a sign of HIV progression or decline in CD4 cell counts (5,11,27).  
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43 292 Weight loss may be due to HIV itself, opportunistic infections, or HIV-associated tumours. Weight  
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45 293 loss in both ART naïve and exposed patients has been associated with increased morbidity and  
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47 294 mortality (28,29,30). A study in England observed that each log<sub>10</sub> increase in HIV viral load was

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3 295 associated with a 0.92 kg decrease in body weight. However, a decrease in viral load was not  
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5 296 significantly associated with weight gain, contrary to our study (30). Since weight changes  
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8 297 correlate with the virological response, losing weight should be viewed as an alarming sign of  
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10 298 virological failure. Monitoring of weight and body mass index prior to ART initiation and during  
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12 299 follow up is a valuable inexpensive way of identifying individuals with possible treatment failure.  
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15 300 Half of the ART-naïve study participants had proteinuria, similar to a report from Zimbabwe (31).  
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17 301 The presence of proteinuria was associated with HIV non-suppression. Proteinuria at six months  
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20 302 was a strong predictor for HIV non-suppression. Proteinuria in HIV-infected individuals is  
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22 303 attributed to a direct effect of HIV on the glomerular and tubular epithelial cells with the  
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24 304 progression of HIV disease to AIDS, nephrotoxicity from ART, the progression of chronic kidney  
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26 305 disease and death (14,33). The higher the viral load, the greater the damage to the kidney (33). We  
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29 306 observed a significant proportion of participants with proteinuria of 2+ or above in WHO HIV  
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31 307 clinical stage IV. This underscores the fact that, as HIV disease advances, the greater the damage  
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34 308 to the kidneys as evidenced by increasing proteinuria. Therefore, routine screening for renal  
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36 309 disease may serve not only as a follow-up of renal disease progression but also for HIV treatment  
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38 310 response monitoring.  
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## 312 **Conclusion**

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47 313 A drop in BMI by more than 5%, persistent lymphopaenia or decrease in total lymphocyte count  
48  
49 314 to lymphopaenia, and proteinuria at six months are associated with HIV non-suppression at 6  
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51 315 months after ART initiation. Scores based on these parameters can serve as alternatives to CD4  
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54 316 cell counts and viral load assessment in facilities with scarcity.  
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3 317 **List of abbreviations**  
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6 318 AIDS: Acquired immunodeficiency syndrome  
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8  
9 319 ART: Antiretroviral therapy  
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11  
12 320 BMI: Body mass index  
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15 321 CD4: Cluster of differentiation 4  
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18 322 HIV: Human immunodeficiency virus  
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21 323 TLC: Total lymphocyte counts  
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24 324 WHO: World Health Organization  
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41  
42

43 331 **Author Contributions**  
44

45  
46 332 Study design: LJ and PM; data collection: LJ and PM; Data analysis and interpretation: LJ, PM,  
47

48 333 BT and EH; Manuscript writing: LJ, PM, BT and EH. All the authors gave final approval of the  
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51 334 manuscript.  
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12  
13

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16  
17 341 **Patient consent for publication**  
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23 343 **Ethics approval**  
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25

26 344 Ethical approval was obtained from the Research and Publications Committee of Muhimbili  
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28 345 University of Health and Allied Sciences (Ref. No. DA.287/298/01A). Permission to conduct the  
29  
30 346 study was obtained from Temeke Municipal Hospital administration. Participants were enrolled  
31  
32 347 after providing written informed consent. The confidentiality of patient information was ensured.  
33  
34 348 Participants without viral suppression at the 6<sup>th</sup> month of follow up were managed according to  
35  
36 349 Tanzania National Guidelines for management of HIV and AIDS.  
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41 350 **Data availability statement**  
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44 351 The dataset analysed during the current study is available upon reasonable request to the  
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46 352 corresponding author.  
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3 356 **Ethics Statement**  
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6 357 Muhimbili University of Health and Allied Sciences Institutional Review Board with reference  
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8 358 number DA287/298/01A/  
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12 360 **References**  
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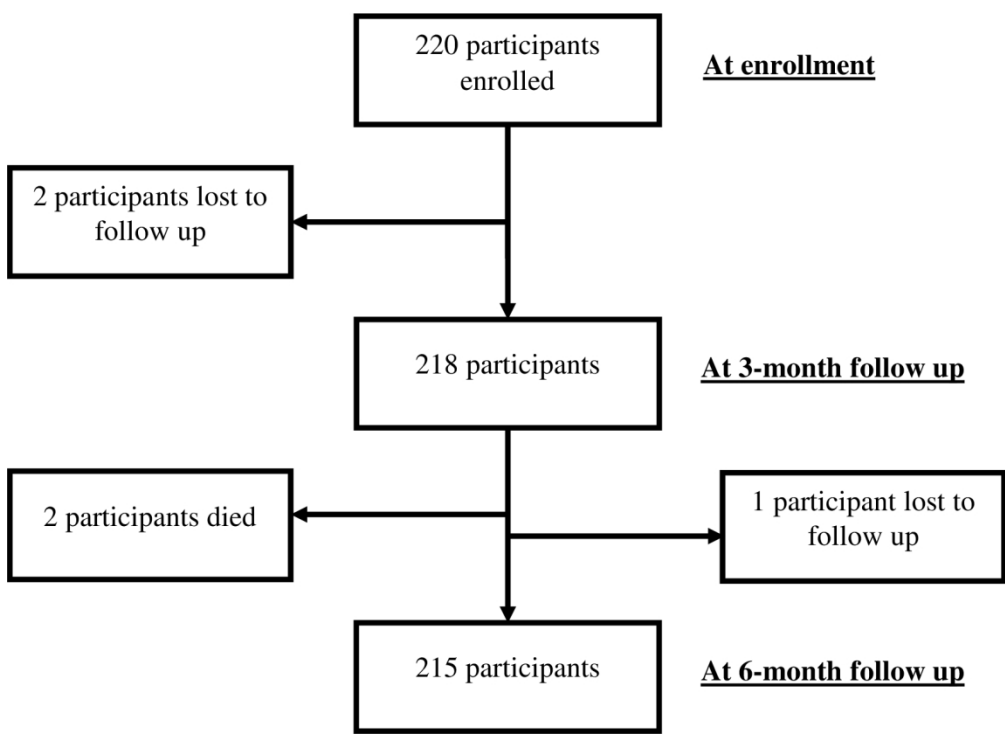


Figure 1. Consort diagram.

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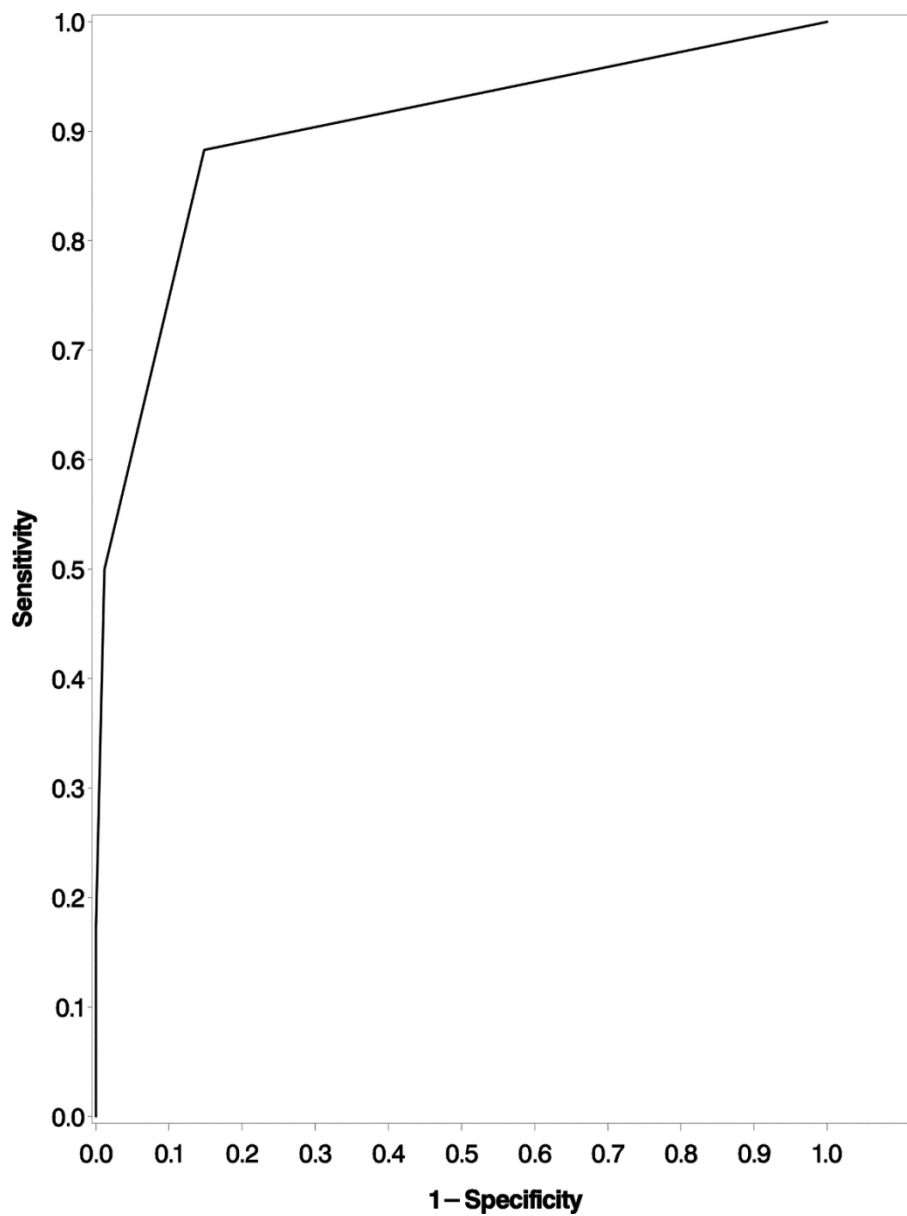
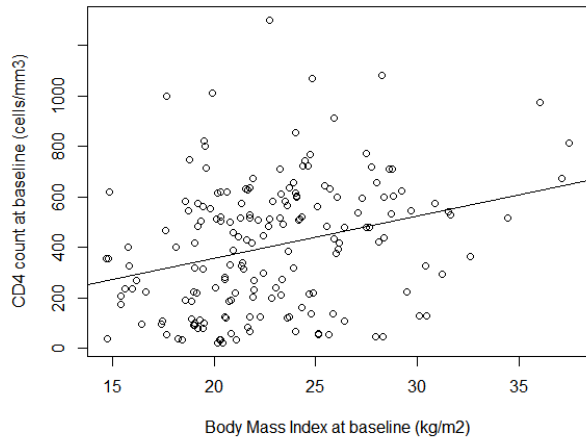


Figure 2. Receiver Operating Characteristic curve assessing a model using BMI decrease, proteinuria, and total lymphocyte counts to predict viral non-suppression among HIV-infected individuals initiated on ART in Dar es Salaam, Tanzania, 2019

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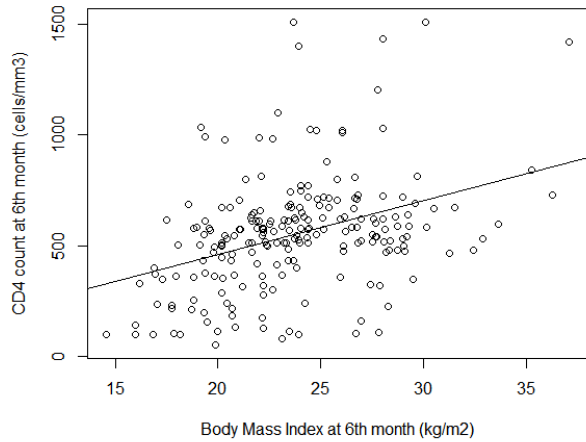
Supplementary Figure 1. Scatter plots of BMI and CD4 counts



rho 0.287, p <0.0001

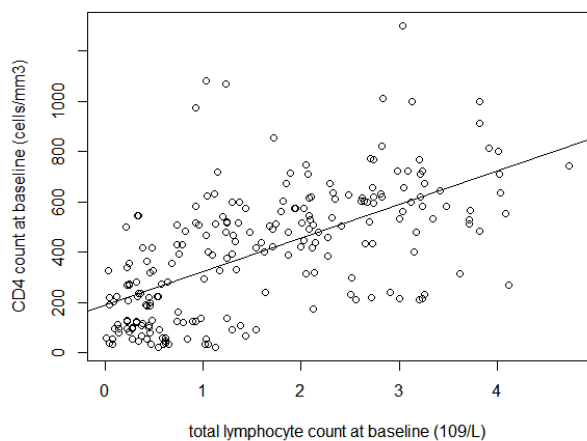


rho 0.305, p <0.0001

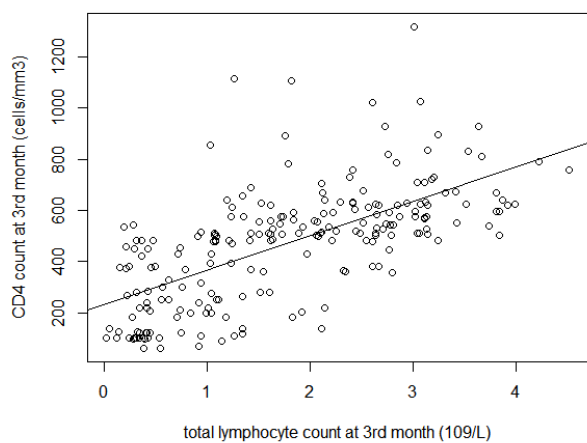


rho 0.373, p <0.0001

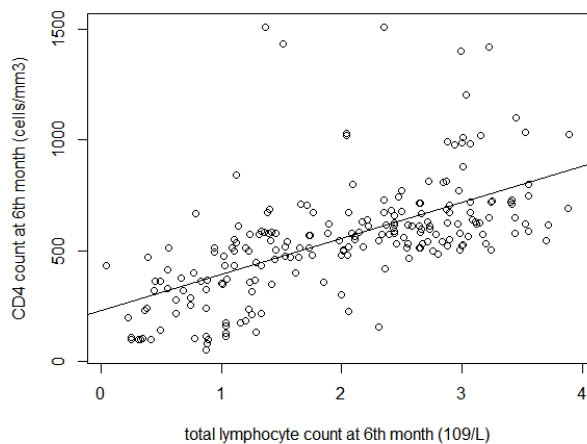
Supplementary Figure 2. Scatter plots of total lymphocyte count and CD4 count



rho 0.613, p <0.0001

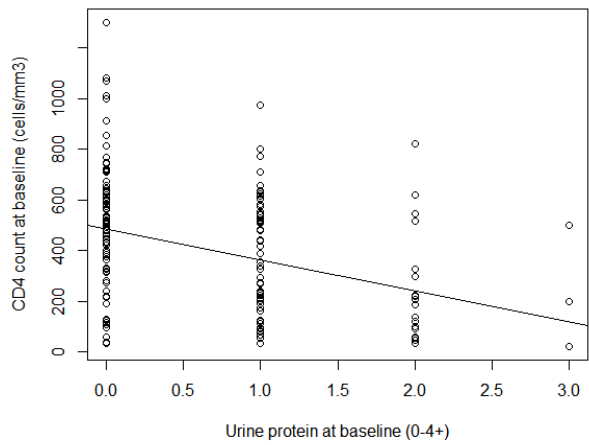


rho 0.650, p <0.0001

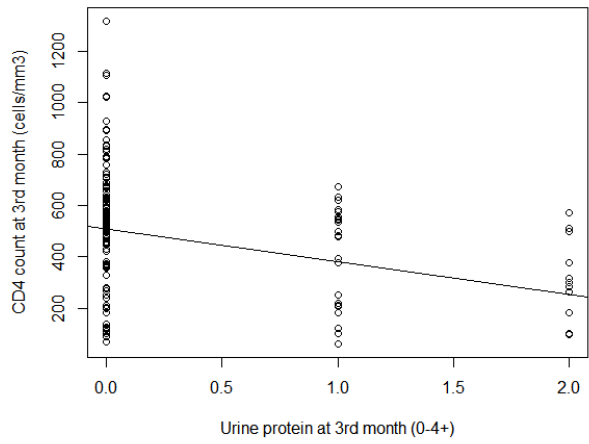


rho 0.602, p <0.0001

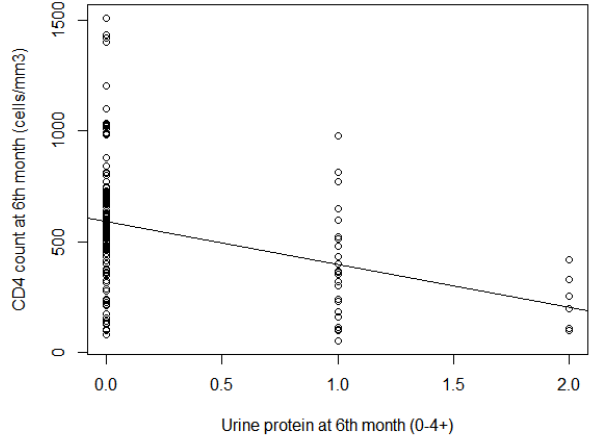
Supplementary Figure 3. Scatter plots of urine protein and CD4 count



rho -0.364, p <0.0001



rho -0.334, p <0.0001



rho -0.372, p <0.0001

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

			Page
		Reporting Item	Number
<b>Title and abstract</b>			
Title	<a href="#">#1a</a>	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and balanced summary	3

of what was done and what was found

## Introduction

Background / [#2](#) Explain the scientific background and rationale for the 6  
 rationale investigation being reported

Objectives [#3](#) State specific objectives, including any prespecified 7  
 hypotheses

## Methods

Study design [#4](#) Present key elements of study design early in the paper 8

Setting [#5](#) Describe the setting, locations, and relevant dates, including 8-10  
 periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and methods of 8-10  
 selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and number of -  
 exposed and unexposed

Variables [#7](#) Clearly define all outcomes, exposures, predictors, potential 9,10  
 confounders, and effect modifiers. Give diagnostic criteria, if  
 applicable

Data sources / [#8](#) For each variable of interest give sources of data and details of 8-10  
 measurement methods of assessment (measurement). Describe  
 comparability of assessment methods if there is more than one  
 group. Give information separately for for exposed and  
 unexposed groups if applicable.

1	Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias	
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4	Study size	<a href="#">#10</a>	Explain how the study size was arrived at	8
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7	Quantitative	<a href="#">#11</a>	Explain how quantitative variables were handled in the	9-11
8	variables		analyses. If applicable, describe which groupings were chosen,	
9			and why	
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15	Statistical	<a href="#">#12a</a>	Describe all statistical methods, including those used to control	
16	methods		for confounding	
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23	Statistical	<a href="#">#12b</a>	Describe any methods used to examine subgroups and	10, 11
24	methods		interactions	
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29	Statistical	<a href="#">#12c</a>	Explain how missing data were addressed	12
30	methods			
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34	Statistical	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed	-
35	methods			
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39	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses	
40	methods			
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48	<b>Results</b>			
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51	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of study—eg	12
52			numbers potentially eligible, examined for eligibility, confirmed	(figure 1)
53			eligible, included in the study, completing follow-up, and	
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unexposed groups if applicable.

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4	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage
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9	Participants	<a href="#">#13c</a>	Consider use of a flow diagram
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12	12 (figure 1)		
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15	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg demographic,
16			clinical, social) and information on exposures and potential
17			confounders. Give information separately for exposed and
18			unexposed groups if applicable.
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25	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data for each
26			variable of interest
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33	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total amount)
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40	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary measures
41			over time. Give information separately for exposed and
42			unexposed groups if applicable.
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50	Main results	<a href="#">#16a</a>	Give unadjusted estimates and, if applicable, confounder-
51			adjusted estimates and their precision (eg, 95% confidence
52			interval). Make clear which confounders were adjusted for and
53			why they were included
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1	Main results	<a href="#">#16b</a>	Report category boundaries when continuous variables were	12-15
2			categorized	
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6	Main results	<a href="#">#16c</a>	If relevant, consider translating estimates of relative risk into	
7			absolute risk for a meaningful time period	
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15	Other analyses	<a href="#">#17</a>	Report other analyses done—eg analyses of subgroups and	16
16			interactions, and sensitivity analyses	
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20	<b>Discussion</b>			
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23	Key results	<a href="#">#18</a>	Summarise key results with reference to study objectives	20
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26	Limitations	<a href="#">#19</a>	Discuss limitations of the study, taking into account sources of	5
27			potential bias or imprecision. Discuss both direction and	
28			magnitude of any potential bias.	
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34	Interpretation	<a href="#">#20</a>	Give a cautious overall interpretation considering objectives,	18-20
35			limitations, multiplicity of analyses, results from similar studies,	
36			and other relevant evidence.	
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42	Generalisability	<a href="#">#21</a>	Discuss the generalisability (external validity) of the study	20
43			results	
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47	<b>Other Information</b>			
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50	Funding	<a href="#">#22</a>	Give the source of funding and the role of the funders for the	22
51			present study and, if applicable, for the original study on which	
52			the present article is based	
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3 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

**Body mass index, proteinuria and total lymphocyte counts in predicting treatment responses among ART naïve individuals with HIV initiated on antiretroviral treatment in Dar es Salaam, Tanzania, 2019: a cohort study**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-059193.R1
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<b>Primary Subject Heading</b>:	HIV/AIDS
Secondary Subject Heading:	HIV/AIDS
Keywords:	INTERNAL MEDICINE, INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES

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3 **1 Body mass index, proteinuria and total lymphocyte counts in predicting treatment**  
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5 **2 responses among ART naïve individuals with HIV initiated on antiretroviral treatment in**  
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7 **3 Dar es Salaam, Tanzania, 2019: a cohort study**  
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14 5 Patricia Munseri<sup>1\*</sup>§, Lazaro Jassely<sup>1\*</sup>, Basil Tumaini<sup>1</sup>, Ellen Hertzmark<sup>2</sup>  
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19 **Keywords:** monitoring ART treatment; HIV/AIDS; CD4 count; BMI in HIV; proteinuria in  
20 HIV; viral suppression

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3 22 **Abstract**  
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6 23 **Objectives:** To explore the potential use of body mass index, proteinuria, and total lymphocyte  
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8 24 count changes in predicting immunological and virological response in individuals with HIV  
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10 25 initiated on antiretroviral therapy (ART).  
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14 26 **Design:** Prospective cohort study.  
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17 27 **Setting:** Three urban HIV care and treatment centres (CTC) in Dar es Salaam.  
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20 28 **Participants:** Individuals with HIV initiating ART.  
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23 29 **Outcome measures:** HIV viral load  $\geq 1000$  copies/ml (viral non-suppression) at six months after  
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25 30 ART initiation.  
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28 31 **Results:** Of 215 (out of 220 enrolled) participants who returned for evaluation at six months, 147  
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30 32 (66.8%) were female. At six months of follow-up, 89.4% (76/85) of participants with sustained  
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32 33 weight gain were virally suppressed compared to 31.8% (7/22) with sustained loss,  $p < 0.001$ . In  
33  
34 34 participants who were lymphopaenic at baseline, an increase to normal total lymphocyte counts at  
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36 35 six months was associated with an increase in CD4 count compared to participants who remained  
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38 36 lymphopaenic, 96.2% (50/52) vs. 54.8% (17/31),  $p < 0.001$ . At baseline, 50.0% (110/220) had  
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40 37 proteinuria. In participants without proteinuria from baseline to six months, 89.8% (79/88) were  
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42 38 virally suppressed compared to participants with proteinuria at baseline and/or three months,  
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44 39 85.6% (77/90), those with persistent proteinuria, 30.8% (8/26), and proteinuria at six months only,  
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46 40 45.5% (5/11),  $p < 0.001$ . In modified Poisson regression, the independent predictors other than CD4  
47  
48 41 cell counts for viral non-suppression at six months among individuals with HIV initiating on ART  
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50 42 were BMI loss  $> 5\%$  from baseline to six months, {adjusted RR 2.73, 95% CI (1.36-5.47)},  
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3 43 lymphopaenia at six months, {adjusted RR = 4.54, 95% CI (2.19-9.39)}, and proteinuria at six  
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5 44 months {adjusted RR = 2.63, 95% CI (1.25-5.54)}.

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8 45 **Conclusions:** Change in body mass index, total lymphocyte count, and presence of proteinuria can  
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10 46 monitor and predict ART response and may be particularly helpful in settings when CD4 counts  
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13 47 and viral load monitoring are unavailable.

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3 **49 Article Summary**  
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6 **50 Strengths and limitations of this study**  
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9 **51** ➤ We had complete data on 98% of the originally enrolled participants.  
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11 **52** ➤ In resource-constrained situations, when viral load and CD4 testing are not always easily  
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13 available, models such as ours with locally determined easily computable prediction cut-offs  
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16 can be utilized by clinicians to make clinical decisions.  
17 **54**  
18 **55** ➤ Our findings require validation in a study with larger sample size.  
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20 **56** ➤ Local conditions and treatment standards may influence some of the patterns we observed,  
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22 both in prevalence and in effect.  
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## Introduction

In 2019 about 38 million people were living with HIV globally, with 1.7 million in Tanzania accounting for an estimated prevalence of 4.8% in the Tanzanian population aged 15-49 years [1]. Viral load testing is the recommended method for monitoring HIV treatment response [2]. However, viral load testing in resource-constrained settings is challenged by limited access, high costs, unavailability at district levels, and in areas where available, sometimes a shortage of reagents, compounded by challenges with equipment maintenance [3], as happened during the COVID-19 pandemic.

There is no doubt that viral load testing is effective in monitoring patient treatment adherence and HIV resistance, as per WHO guidelines. However, in resource-constrained areas that may not always be able to perform viral load testing in a timely manner, there is a need for readily available and routinely assessed objective measures that may predict early viral non-suppression or measures that may help with interim evaluation of patients suspected to have treatment failure who will thereafter need additional follow up with viral load testing. Individuals with HIV are routinely assessed for weight, height, renal function, and complete blood counts before initiation of combined antiretroviral treatment (ART) in resource constrained settings including Tanzania. These assessments are repeated at intervals of three months, six months and biannually after ART initiation. Adverse changes in such parameters from treatment initiation (baseline) or subsequently at follow-up visits provides useful information about treatment responses and may identify a targeted group of patients to be prioritized for viral load testing before a decision to switch the ART regimen.

Routine parameters such as body mass index, total lymphocyte counts, and protein in urine are easily available and can be evaluated in combination for HIV treatment monitoring. Weight loss

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3 82 is one of the major manifestations of advanced HIV infection. Factors hypothesized to contribute  
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5 83 to weight loss include metabolic alterations, anorexia, malabsorptive disorders, hypogonadism,  
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8 84 and excessive cytokine production [4]  
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11 85 Weight gain following ART initiation may reflect slowed resting energy expenditure resulting  
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13 86 from viral suppression and a decrease in HIV enteropathy [5]. Weight gain, especially among  
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15 87 individuals with low BMI, is associated with improved survival and decreased risk of clinical  
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17 88 failure [6]. ART responses depend on adherence [7], nutritional status at baseline [8], HIV subtype  
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19 89 [9], and ART combination regimen [10]. In Port Harcourt, Nigeria, among 318 participants with  
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21 90 HIV infection aged  $\geq 18$  years initiated on ART, almost 70% and 55% of participants gained at  
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23 91 least 1 kg weight in the first six months and one year of treatment, respectively [11]. Previous  
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25 92 studies in Tanzania have shown that a decrease in nutrition status within the first three months of  
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27 93 ART initiation was associated with mortality [12].  
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32 94 HIV-associated nephropathy (HIVAN) is the most common renal biopsy finding in individuals  
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34 95 with HIV with a prevalence ranging from 4.7 to 38% [13]. Proteinuria and elevated creatinine have  
35  
36 96 been associated with AIDS-defining illness and death [14]. Urine assessment for protein by  
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38 97 dipstick can detect renal disease and progression, especially as renal biopsy, an invasive procedure,  
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40 98 is not readily available in most resource-constrained settings.  
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44 99 HIV is associated with progressive destruction of CD4+ T-helper lymphocytes responsible for the  
45  
46 100 profound immunodeficiency that underlies AIDS [15]. As CD4 cells are a subset of lymphocytes,  
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48 101 any significant change in CD4 cells will cause a parallel change in total lymphocyte counts [16].  
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102 This study aimed at assessing the following routinely accessible parameters: body mass index,  
103 proteinuria, and total lymphocyte counts (TLC), and their patterns of change in monitoring HIV  
104 treatment responses at six months following ART initiation.

For peer review only

## 105 **Methods**

### 106 **Study design and population**

107 This cohort study was conducted in three urban care and treatment centres (CTC) in Temeke  
108 district, Dar es Salaam: Temeke regional referral hospital, Mbagala Rangi-tatu district hospital,  
109 and Mbagala Kizuiani dispensary between September 2018 and April 2019. The centres were  
110 chosen due to large numbers of ART naïve clients, amounting to 60 or more per clinic per month.  
111 The sites have an organized CTC and follow up plan for clients. Participants were included in the  
112 study if they were newly diagnosed with HIV and were ART naïve aged 18 years or older and  
113 were able to provide written informed consent. Participants were initiated on ART based on the  
114 Tanzanian National guidelines [17] with a default regimen of tenofovir, lamivudine and efavirenz  
115 unless contraindicated.

### 116 **Sample size estimation**

117 To determine the minimal detectable relative risks for the study variables, we considered two-  
118 sample tests of the expected highest risk category versus the expected lowest risk category. For  
119 the dichotomous potential risk factors, we assumed a total number of 215 subjects, split roughly  
120 as our actual data are split (with numbers rounded to the nearest 5 to mimic a pre-study power  
121 calculation). For BMI change we used 80 for the reference group (gain), 125 for stable, and 20 for  
122 the loss group. The minimum detectable risk ratios were 3.77 for decreased BMI, 2.56 for stable  
123 BMI, 2.94 for lymphopenia and for proteinuria, 2.47 for stage greater than 1, 2.47 for age of 40,  
124 years and above 2.59 (or  $< 0.11$ ) for female sex, 2.74 for secondary or higher education, 2.44 for  
125 unemployment and for never married.

126

## 127 **Data collection**

128 We used an interviewer-based structured tool to conduct face-to-face interviews to obtain socio-  
129 demographic and baseline characteristics (at treatment initiation) such as age, sex, occupation, the  
130 highest level of education attained, marital status, and clinically assessed the participant's WHO  
131 HIV clinical stage. A participant's baseline weight was measured using a SECA weighing scale  
132 recording to the nearest 0.5 kg and height using a wall stadiometer recording to the nearest 0.5 cm.  
133 Body mass index was then computed by dividing the weight in kg by the height in meters squared,  
134 the interpretation of which was adapted from WHO [18].

135 About 10ml of venous blood was collected aseptically from each participant; 5ml for CD4 cell  
136 counts, analysed using BD FACSCount™ (Becton Dickenson, USA) and 5ml for complete blood  
137 count to obtain the total lymphocyte counts, analysed by an auto-analyser (Cell DNY1800 from  
138 Abbott Diagnostics Division, USA). TLC was categorized as lymphopaenia ( $<1 \times 10^9/L$ ), normal  
139 lymphocyte ( $1 \times 10^9/L$  to  $4 \times 10^9/L$ ), and lymphocytosis ( $>4.0 \times 10^9/L$ ). We assessed for proteinuria  
140 by collecting about 15ml of a fresh urine sample from each participant into an empty, clean, dry  
141 container and tested using CYBOW™ strips (DFI Co. Ltd, Korea). Proteinuria was categorized as  
142 negative proteinuria (no proteinuria), trace or 1+ proteinuria (equivalent to 30 to 100 mg/dl), 2+  
143 proteinuria (equivalent to 100 to 300 mg/dl), 3+ proteinuria (equivalent to 300 to 1000 mg/dl), and  
144 4+ proteinuria (equivalent to greater than 1000 mg/dl).

145 At three and six months after ART initiation, a repeat assessment of participants was done for CD4  
146 cell counts, TLC, proteinuria, and weight. At six months, an additional 5ml of blood was collected  
147 from each study participant for viral load measurement using the Abbott RealTime HIV-1 assay.  
148 Participants were classified as virally suppressed at six months after ART initiation if their HIV  
149 viral load was  $<1000$  copies/ml, according to Tanzania HIV treatment guidelines. Levels and

150 changes in BMI, lymphocytes, and proteinuria were compared between participants who were HIV  
151 suppressed and that of HIV not suppressed.

152 BMI was considered to have changed between one time point and another if it increased or  
153 decreased by over 5%. BMI changes from ART initiation to six months were categorized into three  
154 groups as (i) loss of more than 5%, (ii) stable (change between -5% and 5%, or (iii) gain of more  
155 than 5%. The TLC were categorized as (i) lymphopaenia  $< 1 \times 10^9$  cells/L, (ii) normal lymphocyte  
156 count  $1-4 \times 10^9$  cells/L (iii) Lymphocytosis  $> 4 \times 10^9$  cells/L. The TLC pattern change was  
157 categorized as (i) lymphopaenic at 6 months, regardless of the status at baseline or three months;  
158 (ii) increased from lymphopaenic to normal or higher; (iii) stayed normal or higher (no  
159 lymphopaenia seen). Urinary protein patterns were categorized as (i) proteinuria at six months  
160 regardless of baseline proteinuria status; (ii) proteinuria at baseline and/or third month but not six  
161 months; and (iii) no proteinuria seen.

### 162 **Patient and public involvement**

163 Patients or members of the public were not involved in the design, or conduct, or reporting, or  
164 dissemination plans of the research.

### 165 **Statistical methods**

166 Data were analysed using IBM® SPSS® Statistics version 26, R, and SAS version 9.4 (Cary, NC).  
167 Categorical variables such as age group, sex, marital status, level of education, occupation,  
168 categories of BMI, CD4 count, proteinuria, TLC, BMI change, TLC change, and proteinuria  
169 change were summarized as frequencies and proportions. Continuous variables such as age, BMI,  
170 and CD4 count were summarized as means and standard deviations. When necessary, small groups



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3 171 were combined for analysis. To determine the association between BMI, TLC or urine protein to  
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5 172 CD4 count, we used correlation.  
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8 173 To determine the relationships between individual predictors and viral non-suppression at six  
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10 174 months, we first used modified Poisson regression for univariable analysis with an assumption that  
11  
12 175 viral non suppression is a non-rare outcome (more than 10%), to determine which variables to  
13  
14 176 include in the multivariable model [19,20]. For multivariable prediction, all predictors in the  
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16 177 univariable model with a p-value of <0.2 and age, a known confounder, were entered into the  
17  
18 178 modified Poisson regression model. The results of the Poisson regression model were presented  
19  
20 179 as relative risk (RR) and 95% confidence interval (RR; 95% CI). To determine the test  
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22 180 characteristics (sensitivity, specificity, positive predictive value (PPV), negative predictive value  
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24 181 (NPV)) of a score based on the multivariable model, we used two cut-off levels, based on the first  
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26 182 quartile and median of the score among the non-suppressed. The score was the sum of the rounded  
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28 183 coefficients for the variables for which the confidence intervals did not include 1 in a model  
29  
30 184 containing only these variables. Since these all rounded to 1, this is equivalent to simply counting  
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32 185 the number of these characteristics.  
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39 186 Based on practices in low resourced clinics, communication with the patient and the decision to  
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41 187 change the ART regimen depends on the patient's virological status at six months. CD4 cell counts  
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43 188 depend on a blood sample collected at the six-month visit and are therefore unavailable for  
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45 189 immediate decision making. We, therefore, excluded all CD4 variables from the model and used  
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47 190 parameters available at the time of the six-month visit to predict viral non-suppression.  
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## Results

192 During the recruitment, 220 ART naïve individuals with HIV were initiated on ART and all were  
 193 enrolled in the study over a month; each participant was followed up for six months. Two  
 194 participants were lost to follow up at three months; two died before six months of follow up, and  
 195 one participant, a long-distance truck driver, was out of the country at the time of the 6-month  
 196 follow up. Therefore, our analysis data set includes the remaining 215 participants. Details of  
 197 enrolment are shown in Fig 1.

198

199

200 **Figure 1. Consort diagram.**

201

202

### 203 Baseline characteristics of study participants

204 Of the 215 participants analysed, the mean age (SD) was  $37.1 \pm 11.5$  years, 146 (68%) were female,  
 205 113 (53%) were never married, 45 (21%) had secondary education or higher, and 117 (54%) were  
 206 unemployed (Table 1). Most participants, 59.5%, had normal BMI, while 27% were overweight,  
 207 and 13% were underweight. Most participants, 113 (62%), were in WHO HIV clinical stage I, and  
 208 only eight (4%) were in stage IV, though 93 (43%) had CD4 counts of 350 cells/ml or below; 83  
 209 (39%) were lymphopaenic, and 111 (52%) had proteinuria at baseline.

210

211 **Table 1. Characteristics of 215 study participants at ART initiation, Dar es Salaam,**  
 212 **Tanzania, 2019.**

Characteristic	n (%)	Mean $\pm$ SD
Age (years)		$37.1 \pm 11.5$

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2			
3	<b>Age group (years)</b>		
4	18 – 30	69 (32.1%)	
5	31 – 40	72 (33.5%)	
6	41 – 50	45 (20.9%)	
7	>51	29 (13.5%)	
8			
9			
10	<b>Sex</b>		
11	Female	146 (67.9%)	
12	Male	69 (32.1 %)	
13			
14	<b>Level of education</b>		
15	No education	10 (4.7%)	
16	Primary education	160 (74.4%)	
17	Secondary education	42 (19.5%)	
18	Higher education	3 (1.4%)	
19			
20	<b>Employment Status</b>		
21	Not employed	117 (54.4%)	
22	Employed	98 (45.6%)	
23			
24	<b>Marital status</b>		
25	Ever married	102 (47.4%)	
26	Never married	113 (52.6%)	
27			
28	<b>Body mass index (kg/m<sup>2</sup>)</b>		22.9 ± 4.3
29	Underweight	28 (13.0%)	
30	Normal weight	128 (59.5%)	
31	Overweight/Obese	59 (27.4%)	
32			
33	<b>WHO HIV clinical stages</b>		
34	Stage I	133 (61.9%)	
35	Stage II	30 (14.0%)	
36	Stage III	44 (20.5%)	
37	Stage IV	8 (3.7%)	
38			
39	<b>CD4 cell counts (cells/mm<sup>3</sup>)</b>		401 ± 253
40	<200	55 (25.6%)	
41	200-350	38 (17.7%)	
42	351-500	39 (18.1%)	
43	>500	83 (38.6%)	
44			
45	<b>Lymphocyte counts (x10<sup>9</sup>cells/L)</b>		1.6 ± 1.2
46	<1	83 (38.6%)	
47	1-4	126 (58.6%)	
48	>4	6 (2.8%)	
49			
50	<b>Proteinuria</b>		
51	No proteinuria	104 (48.4 %)	
52	1+ (30 – 100 mg/dl)	80 (37.2%)	
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2+ (100 – 300 mg/dl)	27 (12.6%)
3+ (300 – 1000 mg/dl)	4 (1.9%)

213 CD4: Cluster of differentiation 4; HIV: Human Immunodeficiency Virus; SD: Standard Deviation

214

215

216 **Table 2. Predictors of HIV viral load non-suppression at six months among 215 ART naïve**  
 217 **participants initiating ART, Dar es Salaam, Tanzania, 2019.**

Variable	Total	HIV non-suppression at six months n (%)	RR (95% CI)	Adjusted RR (95% CI)
<b>Age (years)</b>				
< 40	136	26 (19%)	1	1
≥40	79	20 (25%)	1.32 (0.79-2.21)	1.43 (0.91-2.26)
<b>Sex</b>				
Female	146	35 (24%)	1.50 (0.81-2.78)	1.27 (0.73-2.20)
Male	69	11 (16%)	1	1
<b>Level of Education</b>				
Primary or less	170	37 (22%)	1	
Secondary or higher	45	9 (20%)	0.92 (0.48-1.76)	
<b>Employment Status</b>				
Not employed	117	24 (21%)	1	
Employed	98	22 (22%)	1.09 (0.66-1.83)	
<b>Marital status</b>				
Never married	113	19 (17%)	1	1
Ever married	102	27 (26%)	1.57 (0.93-2.66)	1.34 (0.84-2.16)
<b>Body mass index</b>				
Change from baseline to three months				
Loss >5%	28	17 (61%)	4.93 (2.41-10.09)	
Stable	122	21 (17%)	1.40 (0.66-2.99)	
Gain >5 %	65	8 (12%)	1	
Change from baseline to six months				
Loss >5%	20	16 (80%)	7.11 (3.69-13.69)	2.73 (1.36-5.47)
Stable	115	21 (18%)	1.62 (0.78-3.36)	1.87 (0.95-3.68)
Gain >5 %	80	9 (11%)	1	1
<b>HIV clinical stage</b>				
I	133	24 (18%)	1	1
II	30	8 (27%)	1.48 (0.74-2.97)	1.14 (0.63-2.08)
III and IV	52	14 (27%)	1.49 (0.84-2.66)	0.82 (0.51-1.31)

<b>Total lymphocyte count change from baseline to six months</b>				
Ended lymphopaenic	37	27 (73%)	7.66 (4.32-13.60)	4.54 (2.19-9.39)
Lymphopaenic to normal	52	7 (13%)	1.41 (0.59-3.40)	1.59 (0.66-3.80)
Lymphopaenia not seen	126	12 (10%)	1	1
<b>Pattern of change in proteinuria</b>				
Proteinuria at 6 months regardless of baseline proteinuria status	37	24 (65%)	6.73 (3.34-13.58)	2.63 (1.25-5.54)
Proteinuria at baseline and/or 3 months but not 6 months	95	14 (15%)	1.53 (0.67-3.47)	1.26 (0.62-2.57)
No proteinuria seen	83	8 (10%)	1	1

218 CI: confidence interval; RR: relative risk; ART: antiretroviral therapy.

219 Univariable and multivariable analysis by modified Poisson regression.

220

221 BMI and CD4 count were directly correlated at baseline, 3, and 6 months. TLC and CD4 count  
 222 were moderately positively correlated; while urine protein and CD4 count were inversely  
 223 correlated (see Supplementary Figures 1, 2, and 3 in Additional file 1).

224

225 **Predictors of viral non-suppression at six months among individuals with HIV initiated on**

226 **ART**

227 Only 46 participants (21%) were not virally suppressed at six months. The strongest clinical  
 228 predictors of viral non-suppression in the multivariable analysis were lymphopaenia at six months  
 229 irrespective of baseline lymphocyte status, with 73% of participants with lymphopaenia at six  
 230 months not being suppressed. After adjusting for other factors, lymphopaenia at six months was  
 231 associated with HIV non-suppression {RR = 4.54, 95% CI (2.19-9.39)}. Among participants with

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3 232 a drop in body mass index at six months of 5% or more from baseline, 80% were non-suppressed  
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5 233 {RR = 2.73; 95% CI (1.36-5.47)}. In an alternative analysis, we considered BMI changes of 10%,  
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7 234 but only 9 of the non-suppressed participants (20%) had such large decreases. The risk of HIV  
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9 235 non-suppression at six months was higher among participants with proteinuria at six months {RR  
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11 236 = 2.63; 95% CI (1.25-5.54)}, Table 2. The area under the Receiver Operating Characteristic (ROC)  
12  
13 237 curve for the multivariable model was 0.895 (Fig 2). Baseline HIV stage was not related to HIV  
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15 238 non-suppression at six months, {adjusted RR = 1.14, 95% CI (0.63-2.08)} for baseline WHO HIV  
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17 239 clinical stage II and {adjusted RR = 0.82, 95% CI (0.51-1.31)} for advanced baseline WHO HIV  
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19 240 clinical stages (III and IV)}.

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24 241 Using the rounded coefficients of the three variables in a model containing only these variables,  
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26 242 which all rounded to 1, we made a “prediction score” with values 0 (n=154, of which 10 were non-  
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28 243 suppressed), 1 (n=36, 13 non-suppressed), 2 (n=17, 15 non-suppressed), and 3 (n=8, all non-  
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30 244 suppressed). The median value of this score among the non-suppressed was 1.5 and the first  
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32 245 quartile value was 1. Thus, having any 2 of the risk factors would be a conservative predictor of  
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34 246 non-suppression, and having any one would be less conservative.  
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3 247 **Figure 2. Receiver Operating Characteristic curve assessing a model using BMI decrease,**  
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5 248 **proteinuria, and total lymphocyte counts to predict viral non-suppression among ART naïve**  
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7 249 **individuals with HIV initiated on ART in Dar es Salaam, Tanzania, 2019**  
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17 252 Using the median score among the non-suppressed as a cut-off (equivalent to having any two of  
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19 253 the components), the sensitivity predicting non-suppression was 0.50, and the specificity was 0.99.

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21 254 Only 12% of the study population met this criterion. When we lowered the cut-off scores to the  
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23 255 first quartile value among the non-suppressed (i.e. any one of the components), the sensitivity was

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26 256 0.78 and the specificity was 0.85, with 28% of the study population meeting this criterion.  
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## 258 Discussion

259 This cohort study recruited ART naïve individuals with HIV from three care and treatment centres  
260 in Dar es Salaam, Tanzania, with the aim of assessing the utility of total lymphocyte count, body  
261 mass index, and proteinuria in predicting ART responses at six months. The intention of this study  
262 is not to replace CD4 cell count testing and HIV viral load monitoring but to assist clinicians when  
263 faced with decision making if these standard monitoring parameters are not easily accessible.  
264 Contrary to earlier studies done when the ART medications were not as effective as the current  
265 ones [12], patient characteristics at ART initiation did not affect the probability of viral non-  
266 suppression at six months, whereas patterns of change and the patient's status at 6 months were  
267 highly predictive.

268 Baseline WHO HIV clinical stage did not help predict HIV non-suppression at six months,  
269 possibly because under the current "Test and Treat" strategy [21], most individuals initiating ART  
270 are in WHO HIV clinical stages I and II (76% of our sample). Current therapy is highly effective  
271 except for a few patients whose disease is so advanced that they die before the medication can  
272 improve their immune status (2 patients in this study). Symptomatic individuals with advanced  
273 HIV will likely adhere to treatment to alleviate their symptoms. Perhaps patients with advanced  
274 disease fear death and therefore are motivated to adhere to ART, with eventual viral suppression.  
275 Advanced HIV disease has been shown to be linked with ART adherence [22]. Some studies,  
276 however, indicate that early HIV stages are linked with high ART adherence and viral suppression  
277 [23].

278 Lymphopaenia at six months, a decrease in body mass index of 5% or more from baseline, and  
279 proteinuria predicted HIV non-suppression at six months. Lymphopaenia at six months was the  
280 strongest predictor for HIV non-suppression at six months. Lymphopaenia at six months predicted



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3 281 HIV non-suppression irrespective of a participant's lymphocyte count (normal or low) before ART  
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5 282 initiation. CD4 cells are a subset of lymphocytes and therefore lymphopaenia could be indicative  
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7 283 of a decline in CD4 cells, as a result of high HIV replication with high viral load signifying viral  
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10 284 non-suppression with consequent CD4 cell destruction. Lymphopaenia was significantly  
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12 285 associated with CD4 <500 cells/mm<sup>3</sup> at all time points. In this study, an increase in total  
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14 286 lymphocyte cell count from lymphopaenia to normal lymphocyte counts from baseline to six  
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17 287 months was significantly associated with an increase in CD4 cell count (Additional file 1). Total  
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19 288 lymphocyte count is sensitive and specific in predicting CD4 cell counts [16][24] though there  
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22 289 have been contradictory reports [25]. The assessment of total lymphocyte counts among patients  
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24 290 on ART, therefore, could serve as an alternative, especially in settings with limited availability of  
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26 291 CD4 cell count measurement. A drop in total lymphocyte count in such a setting can alert a  
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28 292 clinician to the likelihood of immunological failure. A drop in lymphocytes could also signal the  
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31 293 possibility of immunological non responders, who will need primary and secondary prophylaxis  
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33 294 for opportunistic infection.

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36 295 Weight loss with consequent BMI drop of 5% or more at six months while on ART from weight  
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38 296 prior to ART initiation, predicts HIV non-suppression, though HIV non-suppression was not  
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40 297 associated with being underweight prior to ART initiation, perhaps because of the low prevalence  
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43 298 of underweight leading to low power. In this study, sustained weight gain was significantly  
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45 299 associated with viral suppression and sustained weight loss was associated with viral non-  
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48 300 suppression at six months of ART. An increase in weight and hence BMI may be a sign of immune  
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50 301 status improvement signalling a return to health [26] [27]and improved survival [28], while a  
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52 302 decrease in weight and hence BMI may be a sign of HIV progression or decline in CD4 cell counts  
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54 303 [5][11][29]. Weight loss may be due to HIV itself, opportunistic infections, or HIV-associated

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3 304 tumours. Failure to gain weight has been associated with efavirenz toxicity over time as was  
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5 305 observed in a study in South Africa [30]. Weight loss in both ART naïve and exposed patients has  
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7 306 been associated with increased morbidity and mortality [31][32]. A study in England observed that  
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9 307 each log<sub>10</sub> increase in HIV viral load was associated with a 0.92 kg decrease in body weight.  
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11 308 However, a decrease in viral load was not significantly associated with weight gain, contrary to  
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13 309 our study [33]. Since weight changes correlate with the virological response, losing weight should  
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15 310 be viewed as an alarming sign of virological failure. Monitoring of weight and body mass index  
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17 311 prior to ART initiation and during follow up is a valuable inexpensive way of identifying  
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19 312 individuals with possible treatment failure. In an alternative analysis, we considered BMI changes  
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21 313 of 10%, but only 9 of the non-suppressed participants (20%) had such large decreases, making the  
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23 314 10% decrease not useful as a cut-off in our situation.

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29 315 Half of the ART-naïve study participants had proteinuria, similar to a report from Zimbabwe [34].  
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31 316 The presence of proteinuria was associated with HIV non-suppression. Proteinuria at six months  
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33 317 was a strong predictor of HIV non-suppression. Proteinuria in individuals with HIV is attributed  
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35 318 to a direct effect of HIV on the glomerular and tubular epithelial cells with the progression of HIV  
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37 319 disease to AIDS, nephrotoxicity from ART, the progression of chronic kidney disease and death  
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39 320 [14][35]. The higher the viral load, the greater the damage to the kidney [36]. We observed a  
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41 321 significant proportion of participants with proteinuria of 2+ or above in WHO HIV clinical stage  
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43 322 IV. This underscores the fact that, as HIV disease advances, the greater the damage to the kidneys  
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45 323 as evidenced by increasing proteinuria. Therefore, routine screening for renal disease may serve  
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47 324 not only as a follow-up of renal disease progression but also for HIV treatment response  
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49 325 monitoring.  
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3 326 Our findings require validation in a study with a larger sample size. Our small sample may have  
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5 327 constrained some predictors of viral non-suppression. Similar studies conducted in different  
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7 328 locations are also needed since local conditions and treatment standards may influence some  
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10 329 observed patterns, both in prevalence and effect. Furthermore, use of new antiviral drugs and  
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12 330 changes in patient characteristics at presentation may change our estimates, and possibly the  
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14 331 important predictor variables. We recommend further studies to examine the relationship between  
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16 332 virological response and anaemia as well as opportunistic infections and AIDS associated  
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18 333 malignancies especially now that ART is initiated early.

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22 334 One strength of our study is the cohort design with complete follow up data at three and six months  
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24 335 for 98% of the enrolled participants. Although our scoring system is crude, it is easy to compute  
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26 336 and is likely to be valid for a wide variety of situations, whereas a score based on more precise  
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28 337 computations would at best work only in our location.

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### 33 339 **Conclusion**

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38 340 A drop in BMI by more than 5%, persistent lymphopaenia or decrease in total lymphocyte count  
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40 341 to lymphopaenia, and proteinuria at six months are associated with HIV non-suppression at 6  
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42 342 months after ART initiation. Scores based on these parameters are easy to use and can serve as  
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44 343 alternatives to CD4 cell counts and viral load assessment in facilities with scarcity.

### 45 46 47 48 344 **List of abbreviations**

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50  
51 345 AIDS: Acquired immunodeficiency syndrome

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54 346 ART: Antiretroviral therapy

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3 347 BMI: Body mass index  
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6 348 CD4: Cluster of differentiation 4  
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9 349 HIV: Human immunodeficiency virus  
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12 350 TLC: Total lymphocyte counts  
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15 351 WHO: World Health Organization  
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33

34 358 **Author Contributions**  
35

36  
37 359 Study design: LJ and PM; data collection: LJ and PM; Data analysis and interpretation: LJ, PM,  
38  
39 360 BT and EH; Manuscript writing: LJ, PM, BT and EH. All the authors gave final approval of the  
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41 361 manuscript.  
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2  
3 366 **Competing interests**  
4

5  
6 367 None declared.  
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8

9 368 **Patient consent for publication**  
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11  
12 369 Not applicable.  
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14

15 370 **Ethics approval**  
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17  
18 371 Ethical approval was obtained from the Research and Publications Committee of Muhimbili  
19  
20 372 University of Health and Allied Sciences (Ref. No. DA.287/298/01A). Permission to conduct the  
21  
22 373 study was obtained from Temeke Municipal Hospital administration. Participants were enrolled  
23  
24 374 after providing written informed consent. The confidentiality of patient information was ensured.  
25  
26 375 Participants without viral suppression at the 6<sup>th</sup> month of follow up were managed according to  
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28 376 Tanzania National Guidelines for management of HIV and AIDS.  
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32 377 **Data availability statement**  
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35 378 The dataset analysed during the current study is available upon reasonable request to the  
36  
37 379 corresponding author.  
38  
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40  
41 380 **ORCID iDs**  
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46 382 Ellen Hertzmark: <https://orcid.org/0000-0003-0148-2761>  
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48 383 **Ethics Statement**  
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51 384 Muhimbili University of Health and Allied Sciences Institutional Review Board with reference  
52  
53 385 number DA287/298/01A/  
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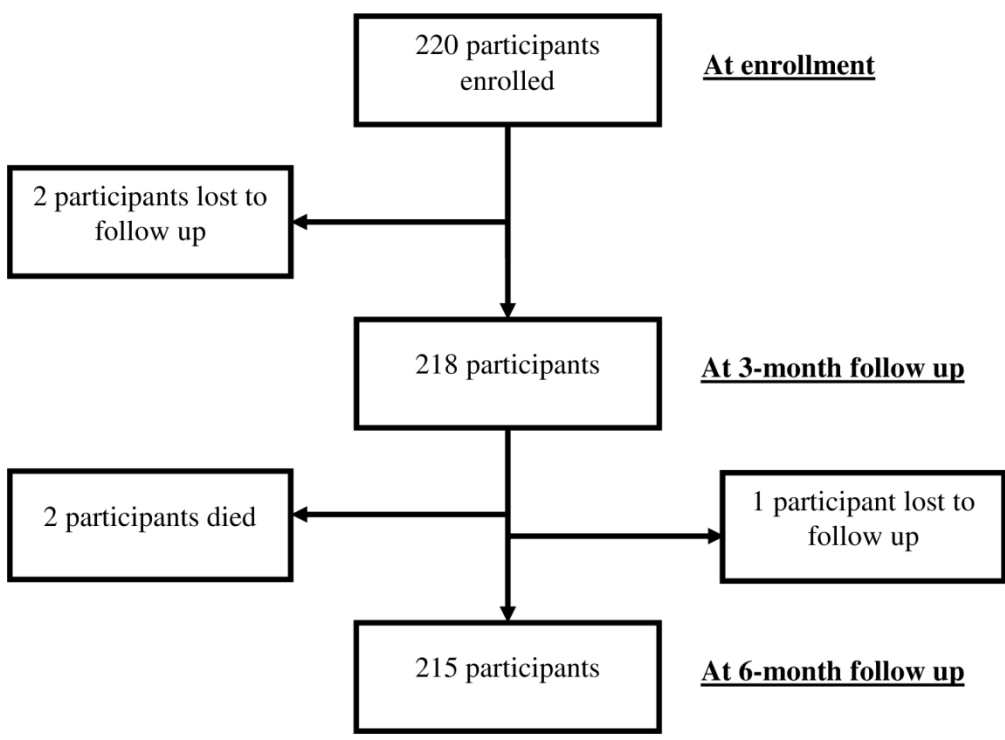


Figure 1. Consort diagram.  
146x105mm (300 x 300 DPI)

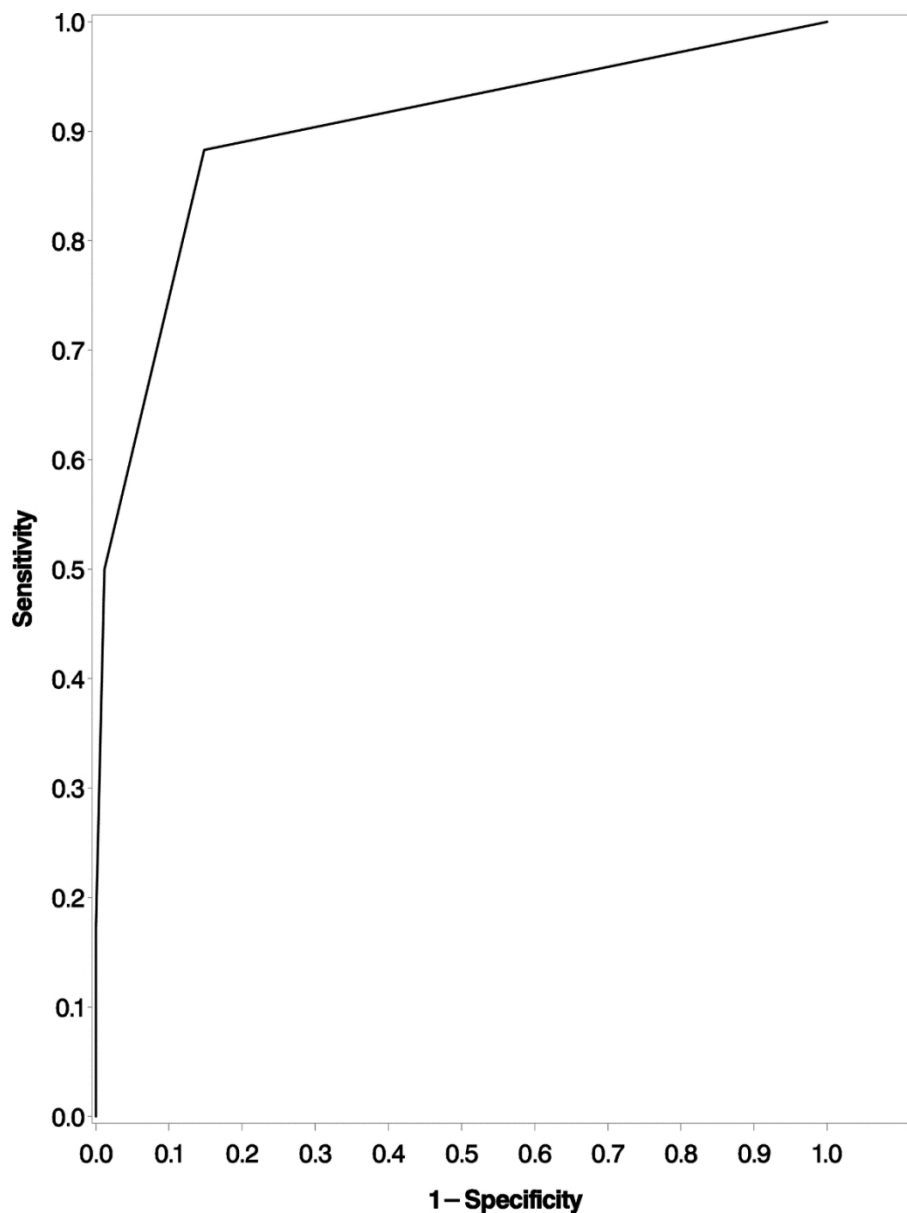
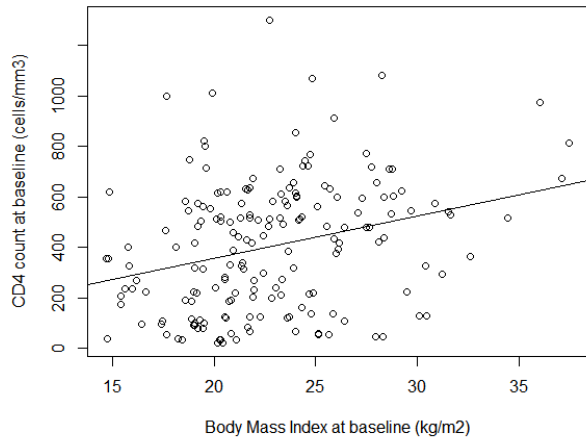


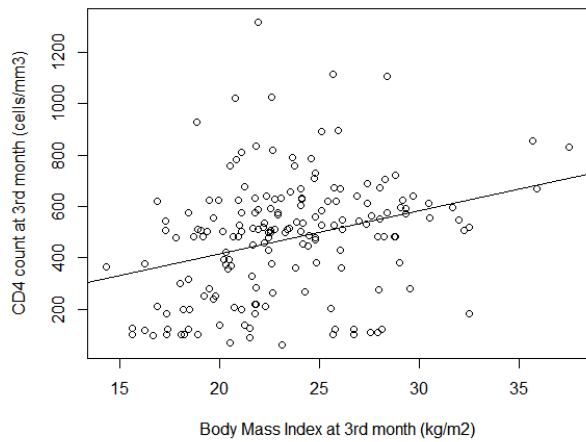
Figure 2. Receiver Operating Characteristic curve assessing a model using BMI decrease, proteinuria, and total lymphocyte counts to predict viral non-suppression among HIV-infected individuals initiated on ART in Dar es Salaam, Tanzania, 2019

137x181mm (220 x 220 DPI)

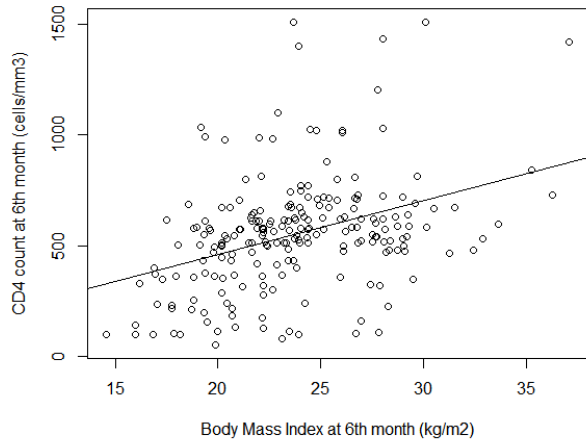
Supplementary Figure 1. Scatter plots of BMI and CD4 counts



rho 0.287, p <0.0001

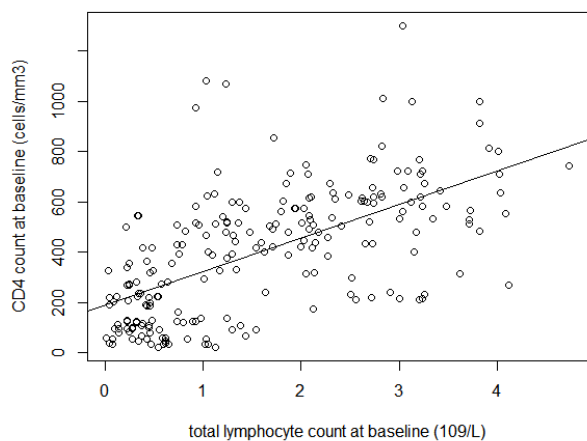


rho 0.305, p <0.0001

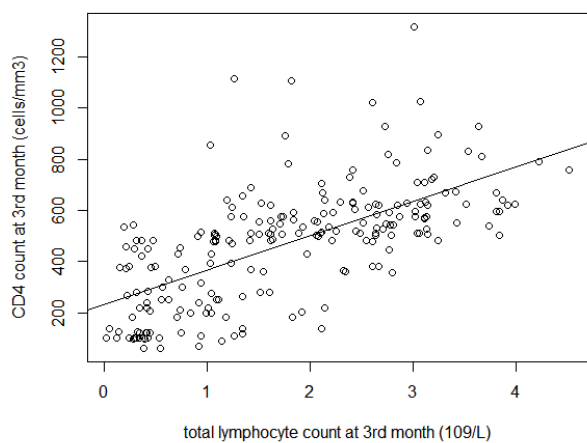


rho 0.373, p <0.0001

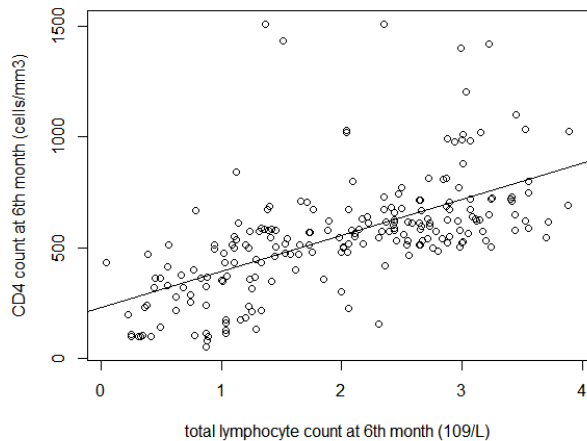
Supplementary Figure 2. Scatter plots of total lymphocyte count and CD4 count



rho 0.613, p <0.0001



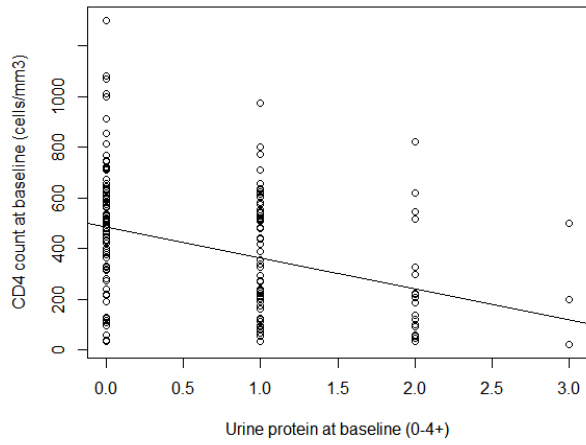
rho 0.650, p <0.0001



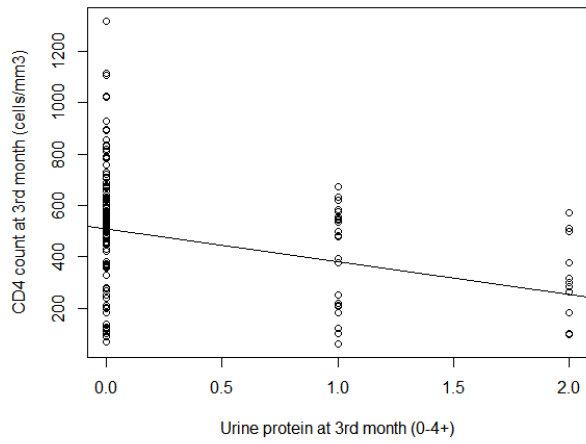
rho 0.602, p <0.0001



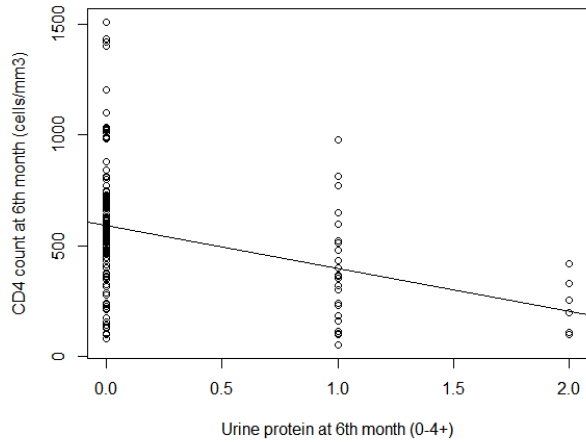
Supplementary Figure 3. Scatter plots of urine protein and CD4 count



rho -0.364, p <0.0001



rho -0.334, p <0.0001



rho -0.372, p <0.0001

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

			Page
		Reporting Item	Number
<b>Title and abstract</b>			
Title	<a href="#">#1a</a>	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and balanced summary	3

of what was done and what was found

## Introduction

Background / [#2](#) Explain the scientific background and rationale for the 6  
 rationale investigation being reported

Objectives [#3](#) State specific objectives, including any prespecified 7  
 hypotheses

## Methods

Study design [#4](#) Present key elements of study design early in the paper 8

Setting [#5](#) Describe the setting, locations, and relevant dates, including 8-10  
 periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and methods of 8-10  
 selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and number of -  
 exposed and unexposed

Variables [#7](#) Clearly define all outcomes, exposures, predictors, potential 9,10  
 confounders, and effect modifiers. Give diagnostic criteria, if  
 applicable

Data sources / [#8](#) For each variable of interest give sources of data and details of 8-10  
 measurement methods of assessment (measurement). Describe  
 comparability of assessment methods if there is more than one  
 group. Give information separately for for exposed and  
 unexposed groups if applicable.

1	Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias	
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4	Study size	<a href="#">#10</a>	Explain how the study size was arrived at	8
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7	Quantitative	<a href="#">#11</a>	Explain how quantitative variables were handled in the	9-11
8	variables		analyses. If applicable, describe which groupings were chosen,	
9			and why	
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15	Statistical	<a href="#">#12a</a>	Describe all statistical methods, including those used to control	
16	methods		for confounding	
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20	10,11			
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23	Statistical	<a href="#">#12b</a>	Describe any methods used to examine subgroups and	10, 11
24	methods		interactions	
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29	Statistical	<a href="#">#12c</a>	Explain how missing data were addressed	12
30	methods			
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34	Statistical	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed	-
35	methods			
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39	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses	
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48	<b>Results</b>			
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51	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of study—eg	12
52			numbers potentially eligible, examined for eligibility, confirmed	(figure 1)
53			eligible, included in the study, completing follow-up, and	
54			analysed. Give information separately for for exposed and	
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unexposed groups if applicable.

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4	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage
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7			(figure 1)
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9	Participants	<a href="#">#13c</a>	Consider use of a flow diagram
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12	12 (figure 1)		
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15	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg demographic,
16			clinical, social) and information on exposures and potential
17			confounders. Give information separately for exposed and
18			unexposed groups if applicable.
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25	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data for each
26			variable of interest
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30	See 12		
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33	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total amount)
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39	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary measures
40			over time. Give information separately for exposed and
41			unexposed groups if applicable.
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50	Main results	<a href="#">#16a</a>	Give unadjusted estimates and, if applicable, confounder-
51			adjusted estimates and their precision (eg, 95% confidence
52			interval). Make clear which confounders were adjusted for and
53			why they were included
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1	Main results	<a href="#">#16b</a>	Report category boundaries when continuous variables were	12-15
2			categorized	
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6	Main results	<a href="#">#16c</a>	If relevant, consider translating estimates of relative risk into	
7			absolute risk for a meaningful time period	
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15	Other analyses	<a href="#">#17</a>	Report other analyses done—eg analyses of subgroups and	16
16			interactions, and sensitivity analyses	
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20	<b>Discussion</b>			
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23	Key results	<a href="#">#18</a>	Summarise key results with reference to study objectives	20
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26	Limitations	<a href="#">#19</a>	Discuss limitations of the study, taking into account sources of	5
27			potential bias or imprecision. Discuss both direction and	
28			magnitude of any potential bias.	
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34	Interpretation	<a href="#">#20</a>	Give a cautious overall interpretation considering objectives,	18-20
35			limitations, multiplicity of analyses, results from similar studies,	
36			and other relevant evidence.	
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42	Generalisability	<a href="#">#21</a>	Discuss the generalisability (external validity) of the study	20
43			results	
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47	<b>Other Information</b>			
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50	Funding	<a href="#">#22</a>	Give the source of funding and the role of the funders for the	22
51			present study and, if applicable, for the original study on which	
52			the present article is based	
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# BMJ Open

**Body mass index, proteinuria and total lymphocyte counts in predicting treatment responses among ART naïve individuals with HIV initiated on antiretroviral treatment in Dar es Salaam, Tanzania, 2019: a cohort study**

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<b>Primary Subject Heading</b>:	HIV/AIDS
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Keywords:	INTERNAL MEDICINE, INFECTIOUS DISEASES, HIV & AIDS < INFECTIOUS DISEASES

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3 **1 Body mass index, proteinuria and total lymphocyte counts in predicting treatment**  
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5 **2 responses among ART naïve individuals with HIV initiated on antiretroviral treatment in**  
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7 **3 Dar es Salaam, Tanzania, 2019: a cohort study**  
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14 5 Patricia Munseri<sup>1\*</sup>§, Lazaro Jassely<sup>1\*</sup>, Basil Tumaini<sup>1</sup>, Ellen Hertzmark<sup>2</sup>  
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19 **Keywords:** monitoring ART treatment; HIV/AIDS; CD4 count; BMI in HIV; proteinuria in  
20 HIV; viral suppression

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3 **Abstract**  
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6 **Objectives:** To explore the potential use of body mass index, proteinuria, and total lymphocyte  
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count changes in predicting immunological and virological response in individuals with HIV initiated on antiretroviral therapy (ART).

**Design:** Prospective cohort study.

**Setting:** Three urban HIV care and treatment centres (CTC) in Dar es Salaam.

**Participants:** Individuals with HIV initiating ART.

**Outcome measures:** HIV viral load  $\geq 1000$  copies/ml (viral non-suppression) at six months after ART initiation.

**Results:** Of 215 (out of 220 enrolled) participants who returned for evaluation at six months, 147 (66.8%) were female. At six months of follow-up, 89.4% (76/85) of participants with sustained weight gain were virally suppressed compared to 31.8% (7/22) with sustained loss,  $p < 0.001$ . In participants who were lymphopaenic at baseline, an increase to normal total lymphocyte counts at six months was associated with an increase in CD4 count compared to participants who remained lymphopaenic, 96.2% (50/52) vs. 54.8% (17/31),  $p < 0.001$ . At baseline, 50.0% (110/220) had proteinuria. In participants without proteinuria from baseline to six months, 89.8% (79/88) were virally suppressed compared to participants with proteinuria at baseline and/or three months, 85.6% (77/90), those with persistent proteinuria, 30.8% (8/26), and proteinuria at six months only, 45.5% (5/11),  $p < 0.001$ . In modified Poisson regression, the independent predictors other than CD4 cell counts for viral non-suppression at six months among individuals with HIV initiating on ART were BMI loss  $> 5\%$  from baseline to six months, {adjusted RR 2.73, 95% CI (1.36-5.47)},

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3 43 lymphopaenia at six months, {adjusted RR = 4.54, 95% CI (2.19-9.39)}, and proteinuria at six  
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5 44 months {adjusted RR = 2.63, 95% CI (1.25-5.54)}.

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8 45 **Conclusions:** Change in body mass index, total lymphocyte count, and presence of proteinuria can  
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10 46 monitor and predict ART response and may be particularly helpful in settings when CD4 counts  
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13 47 and viral load monitoring are unavailable.

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3 **49 Article Summary**  
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6 **50 Strengths and limitations of this study**  
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9 **51** ➤ We had complete data on 98% of the originally enrolled participants.  
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11 **52** ➤ In resource-constrained situations, when viral load and CD4 testing are not always easily  
12 available, models such as ours with locally determined easily computable prediction cut-offs  
13 **53** can be utilized by clinicians to make clinical decisions.  
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15 **54** ➤ Our findings require validation in a study with larger sample size.  
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17 **55** ➤ Local conditions and treatment standards may influence some of the patterns we observed,  
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19 **56** both in prevalence and in effect.  
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## Introduction

In 2019 about 38 million people were living with HIV globally, with 1.7 million in Tanzania accounting for an estimated prevalence of 4.8% in the Tanzanian population aged 15-49 years [1]. Viral load testing is the recommended method for monitoring HIV treatment response [2]. However, viral load testing in resource-constrained settings is challenged by limited access, high costs, unavailability at district levels, and in areas where available, sometimes a shortage of reagents, compounded by challenges with equipment maintenance [3], as happened during the COVID-19 pandemic.

There is no doubt that viral load testing is effective in monitoring patient treatment adherence and HIV resistance, as per WHO guidelines. However, in resource-constrained areas that may not always be able to perform viral load testing in a timely manner, there is a need for readily available and routinely assessed objective measures that may predict early viral non-suppression or measures that may help with interim evaluation of patients suspected to have treatment failure who will thereafter need additional follow up with viral load testing. Individuals with HIV are routinely assessed for weight, height, renal function, and complete blood counts before initiation of combined antiretroviral treatment (ART) in resource constrained settings including Tanzania. These assessments are repeated at intervals of three months, six months and biannually after ART initiation. Adverse changes in such parameters from treatment initiation (baseline) or subsequently at follow-up visits provides useful information about treatment responses and may identify a targeted group of patients to be prioritized for viral load testing before a decision to switch the ART regimen.

Routine parameters such as body mass index, total lymphocyte counts, and protein in urine are easily available and can be evaluated in combination for HIV treatment monitoring. Weight loss

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3 82 is one of the major manifestations of advanced HIV infection. Factors hypothesized to contribute  
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5 83 to weight loss include metabolic alterations, anorexia, malabsorptive disorders, hypogonadism,  
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8 84 and excessive cytokine production [4]  
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10  
11 85 Weight gain following ART initiation may reflect slowed resting energy expenditure resulting  
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13 86 from viral suppression and a decrease in HIV enteropathy [5]. Weight gain, especially among  
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15 87 individuals with low BMI, is associated with improved survival and decreased risk of clinical  
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17 88 failure [6]. ART responses depend on adherence [7], nutritional status at baseline [8], HIV subtype  
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19 89 [9], and ART combination regimen [10]. In Port Harcourt, Nigeria, among 318 participants with  
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21 90 HIV infection aged  $\geq 18$  years initiated on ART, almost 70% and 55% of participants gained at  
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23 91 least 1 kg weight in the first six months and one year of treatment, respectively [11]. Previous  
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25 92 studies in Tanzania have shown that a decrease in nutrition status within the first three months of  
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27 93 ART initiation was associated with mortality [12].  
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32 94 HIV-associated nephropathy (HIVAN) is the most common renal biopsy finding in individuals  
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34 95 with HIV with a prevalence ranging from 4.7 to 38% [13]. Proteinuria and elevated creatinine have  
35  
36 96 been associated with AIDS-defining illness and death [14]. Urine assessment for protein by  
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38 97 dipstick can detect renal disease and progression, especially as renal biopsy, an invasive procedure,  
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40 98 is not readily available in most resource-constrained settings.  
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44 99 HIV is associated with progressive destruction of CD4+ T-helper lymphocytes responsible for the  
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46 100 profound immunodeficiency that underlies AIDS [15]. As CD4 cells are a subset of lymphocytes,  
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48 101 any significant change in CD4 cells will cause a parallel change in total lymphocyte counts [16].  
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3 102 This study aimed at assessing the following routinely accessible parameters: body mass index,  
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5 103 proteinuria, and total lymphocyte counts (TLC), and their patterns of change in monitoring HIV  
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8 104 treatment responses at six months following ART initiation.  
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## 105 **Methods**

### 106 **Study design and population**

107 This cohort study was conducted in three urban care and treatment centres (CTC) in Temeke  
108 district, Dar es Salaam: Temeke regional referral hospital, Mbagala Rangi-tatu district hospital,  
109 and Mbagala Kizuiani dispensary between September 2018 and April 2019. The centres were  
110 chosen due to large numbers of ART naïve clients, amounting to 60 or more per clinic per month.  
111 The sites have an organized CTC and follow up plan for clients. Participants were included in the  
112 study if they were newly diagnosed with HIV and were ART naïve aged 18 years or older and  
113 were able to provide written informed consent. Participants were initiated on ART based on the  
114 Tanzanian National guidelines [17] with a default regimen of tenofovir, lamivudine and efavirenz  
115 unless contraindicated.

### 116 **Sample size estimation**

117 To determine the minimal detectable relative risks for the study variables, we considered two-  
118 sample tests of the expected highest risk category versus the expected lowest risk category. For  
119 the dichotomous potential risk factors, we assumed a total number of 215 subjects, split roughly  
120 as our actual data are split (with numbers rounded to the nearest 5 to mimic a pre-study power  
121 calculation). For BMI change we used 80 for the reference group (gain), 125 for stable, and 20 for  
122 the loss group. The minimum detectable risk ratios were 3.77 for decreased BMI, 2.56 for stable  
123 BMI, 2.94 for lymphopenia and for proteinuria, 2.47 for stage greater than 1, 2.47 for age of 40,  
124 years and above 2.59 (or  $< 0.11$ ) for female sex, 2.74 for secondary or higher education, 2.44 for  
125 unemployment and for never married.

126

## 127 **Data collection**

128 We used an interviewer-based structured tool to conduct face-to-face interviews to obtain socio-  
129 demographic and baseline characteristics (at treatment initiation) such as age, sex, occupation, the  
130 highest level of education attained, marital status, and clinically assessed the participant's WHO  
131 HIV clinical stage. A participant's baseline weight was measured using a SECA weighing scale  
132 recording to the nearest 0.5 kg and height using a wall stadiometer recording to the nearest 0.5 cm.  
133 Body mass index was then computed by dividing the weight in kg by the height in meters squared,  
134 the interpretation of which was adapted from WHO [18].

135 About 10ml of venous blood was collected aseptically from each participant; 5ml for CD4 cell  
136 counts, analysed using BD FACSCount™ (Becton Dickinson, USA) and 5ml for complete blood  
137 count to obtain the total lymphocyte counts, analysed by an auto-analyser (Cell DNY1800 from  
138 Abbott Diagnostics Division, USA). TLC was categorized as lymphopaenia ( $<1 \times 10^9/L$ ), normal  
139 lymphocyte ( $1 \times 10^9/L$  to  $4 \times 10^9/L$ ), and lymphocytosis ( $>4.0 \times 10^9/L$ ). We assessed for proteinuria  
140 by collecting about 15ml of a fresh urine sample from each participant into an empty, clean, dry  
141 container and tested using CYBOW™ strips (DFI Co. Ltd, Korea). Proteinuria was categorized as  
142 negative proteinuria (no proteinuria), trace or 1+ proteinuria (equivalent to 30 to 100 mg/dl), 2+  
143 proteinuria (equivalent to 100 to 300 mg/dl), 3+ proteinuria (equivalent to 300 to 1000 mg/dl), and  
144 4+ proteinuria (equivalent to greater than 1000 mg/dl).

145 At three and six months after ART initiation, a repeat assessment of participants was done for CD4  
146 cell counts, TLC, proteinuria, and weight. At six months, an additional 5ml of blood was collected  
147 from each study participant for viral load measurement using the Abbott RealTime HIV-1 assay.  
148 Participants were classified as virally suppressed at six months after ART initiation if their HIV  
149 viral load was  $<1000$  copies/ml, according to Tanzania HIV treatment guidelines. Levels and

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3 150 changes in BMI, lymphocytes, and proteinuria were compared between participants who were HIV  
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5 151 suppressed and that of HIV not suppressed.  
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8 152 BMI was considered to have changed between one time point and another if it increased or  
9  
10 153 decreased by over 5%. BMI changes from ART initiation to six months were categorized into three  
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12 154 groups as (i) loss of more than 5%, (ii) stable (change between -5% and 5%, or (iii) gain of more  
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14 155 than 5%. The TLC were categorized as (i) lymphopaenia <  $1 \times 10^9$  cells/L, (ii) normal lymphocyte  
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16 156 count  $1-4 \times 10^9$  cells/L (iii) Lymphocytosis >  $4 \times 10^9$  cells/L. The TLC pattern change was  
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18 157 categorized as (i) lymphopaenic at 6 months, regardless of the status at baseline or three months;  
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20 158 (ii) increased from lymphopaenic to normal or higher; (iii) stayed normal or higher (no  
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22 159 lymphopaenia seen). Urinary protein patterns were categorized as (i) proteinuria at six months  
23  
24 160 regardless of baseline proteinuria status; (ii) proteinuria at baseline and/or third month but not six  
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26 161 months; and (iii) no proteinuria seen.  
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### 32 162 **Patient and public involvement**

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35 163 Patients or members of the public were not involved in the design, or conduct, or reporting, or  
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37 164 dissemination plans of the research.  
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### 40 165 **Statistical methods**

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43 166 Data were analysed using IBM® SPSS® Statistics version 26, R, and SAS version 9.4 (Cary, NC).  
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45 167 Categorical variables such as age group, sex, marital status, level of education, occupation,  
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47 168 categories of BMI, CD4 count, proteinuria, TLC, BMI change, TLC change, and proteinuria  
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49 169 change were summarized as frequencies and proportions. Continuous variables such as age, BMI,  
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51 170 and CD4 count were summarized as means and standard deviations. When necessary, small groups  
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3 171 were combined for analysis. To determine the association between BMI, TLC or urine protein to  
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5 172 CD4 count, we used correlation.  
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8 173 To determine the relationships between individual predictors and viral non-suppression at six  
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10 174 months, we first used modified Poisson regression for univariable analysis with an assumption that  
11  
12 175 viral non suppression is a non-rare outcome (more than 10%), to determine which variables to  
13  
14 176 include in the multivariable model [19,20]. For multivariable prediction, all predictors in the  
15  
16 177 univariable model with a p-value of <0.2 and age, a known confounder, were entered into the  
17  
18 178 modified Poisson regression model. The results of the Poisson regression model were presented  
19  
20 179 as relative risk (RR) and 95% confidence interval (RR; 95% CI). To determine the test  
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22 180 characteristics (sensitivity, specificity, positive predictive value (PPV), negative predictive value  
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24 181 (NPV)) of a score based on the multivariable model, we used two cut-off levels, based on the first  
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26 182 quartile and median of the score among the non-suppressed. The score was the sum of the rounded  
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28 183 coefficients for the variables for which the confidence intervals did not include 1 in a model  
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30 184 containing only these variables. Since these all rounded to 1, this is equivalent to simply counting  
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32 185 the number of these characteristics.  
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39 186 Based on practices in low resourced clinics, communication with the patient and the decision to  
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41 187 change the ART regimen depends on the patient's virological status at six months. CD4 cell counts  
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43 188 depend on a blood sample collected at the six-month visit and are therefore unavailable for  
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45 189 immediate decision making. We, therefore, excluded all CD4 variables from the model and used  
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47 190 parameters available at the time of the six-month visit to predict viral non-suppression.  
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## Results

192 During the recruitment, 220 ART naïve individuals with HIV were initiated on ART and all were  
 193 enrolled in the study over a month; each participant was followed up for six months. Two  
 194 participants were lost to follow up at three months; two died before six months of follow up, and  
 195 one participant, a long-distance truck driver, was out of the country at the time of the 6-month  
 196 follow up. Therefore, our analysis data set includes the remaining 215 participants. Details of  
 197 enrolment are shown in Fig 1.

198

199

200 **Figure 1. Consort diagram.**

201

202

### 203 Baseline characteristics of study participants

204 Of the 215 participants analysed, the mean age (SD) was  $37.1 \pm 11.5$  years, 146 (68%) were female,  
 205 113 (53%) were never married, 45 (21%) had secondary education or higher, and 117 (54%) were  
 206 unemployed (Table 1). Most participants, 59.5%, had normal BMI, while 27% were overweight,  
 207 and 13% were underweight. Most participants, 113 (62%), were in WHO HIV clinical stage I, and  
 208 only eight (4%) were in stage IV, though 93 (43%) had CD4 counts of 350 cells/ml or below; 83  
 209 (39%) were lymphopaenic, and 111 (52%) had proteinuria at baseline.

210

211 **Table 1. Characteristics of 215 study participants at ART initiation, Dar es Salaam,**  
 212 **Tanzania, 2019.**

Characteristic	n (%)	Mean $\pm$ SD
Age (years)		$37.1 \pm 11.5$

1			
2			
3	<b>Age group (years)</b>		
4	18 – 30	69 (32.1%)	
5	31 – 40	72 (33.5%)	
6	41 – 50	45 (20.9%)	
7	>51	29 (13.5%)	
8			
9			
10	<b>Sex</b>		
11	Female	146 (67.9%)	
12	Male	69 (32.1 %)	
13			
14	<b>Level of education</b>		
15	No education	10 (4.7%)	
16	Primary education	160 (74.4%)	
17	Secondary education	42 (19.5%)	
18	Higher education	3 (1.4%)	
19			
20	<b>Employment Status</b>		
21	Not employed	117 (54.4%)	
22	Employed	98 (45.6%)	
23			
24	<b>Marital status</b>		
25	Ever married	102 (47.4%)	
26	Never married	113 (52.6%)	
27			
28	<b>Body mass index (kg/m<sup>2</sup>)</b>		22.9 ± 4.3
29	Underweight	28 (13.0%)	
30	Normal weight	128 (59.5%)	
31	Overweight/Obese	59 (27.4%)	
32			
33	<b>WHO HIV clinical stages</b>		
34	Stage I	133 (61.9%)	
35	Stage II	30 (14.0%)	
36	Stage III	44 (20.5%)	
37	Stage IV	8 (3.7%)	
38			
39	<b>CD4 cell counts (cells/mm<sup>3</sup>)</b>		401 ± 253
40	<200	55 (25.6%)	
41	200-350	38 (17.7%)	
42	351-500	39 (18.1%)	
43	>500	83 (38.6%)	
44			
45	<b>Lymphocyte counts (x10<sup>9</sup>cells/L)</b>		1.6 ± 1.2
46	<1	83 (38.6%)	
47	1-4	126 (58.6%)	
48	>4	6 (2.8%)	
49			
50	<b>Proteinuria</b>		
51	No proteinuria	104 (48.4 %)	
52	1+ (30 – 100 mg/dl)	80 (37.2%)	
53			
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2+ (100 – 300 mg/dl)	27 (12.6%)
3+ (300 – 1000 mg/dl)	4 (1.9%)

213 CD4: Cluster of differentiation 4; HIV: Human Immunodeficiency Virus; SD: Standard Deviation

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215

216 **Table 2. Predictors of HIV viral load non-suppression at six months among 215 ART naïve**  
 217 **participants initiating ART, Dar es Salaam, Tanzania, 2019.**

Variable	Total	HIV non-suppression at six months n (%)	RR (95% CI)	Adjusted RR (95% CI)
<b>Age (years)</b>				
< 40	136	26 (19%)	1	1
≥40	79	20 (25%)	1.32 (0.79-2.21)	1.43 (0.91-2.26)
<b>Sex</b>				
Female	146	35 (24%)	1.50 (0.81-2.78)	1.27 (0.73-2.20)
Male	69	11 (16%)	1	1
<b>Level of Education</b>				
Primary or less	170	37 (22%)	1	
Secondary or higher	45	9 (20%)	0.92 (0.48-1.76)	
<b>Employment Status</b>				
Not employed	117	24 (21%)	1	
Employed	98	22 (22%)	1.09 (0.66-1.83)	
<b>Marital status</b>				
Never married	113	19 (17%)	1	1
Ever married	102	27 (26%)	1.57 (0.93-2.66)	1.34 (0.84-2.16)
<b>Body mass index</b>				
Change from baseline to three months				
Loss >5%	28	17 (61%)	4.93 (2.41-10.09)	
Stable	122	21 (17%)	1.40 (0.66-2.99)	
Gain >5 %	65	8 (12%)	1	
Change from baseline to six months				
Loss >5%	20	16 (80%)	7.11 (3.69-13.69)	2.73 (1.36-5.47)
Stable	115	21 (18%)	1.62 (0.78-3.36)	1.87 (0.95-3.68)
Gain >5 %	80	9 (11%)	1	1
<b>HIV clinical stage</b>				
I	133	24 (18%)	1	1
II	30	8 (27%)	1.48 (0.74-2.97)	1.14 (0.63-2.08)
III and IV	52	14 (27%)	1.49 (0.84-2.66)	0.82 (0.51-1.31)



<b>Total lymphocyte count change from baseline to six months</b>				
Ended lymphopaenic	37	27 (73%)	7.66 (4.32-13.60)	4.54 (2.19-9.39)
Lymphopaenic to normal	52	7 (13%)	1.41 (0.59-3.40)	1.59 (0.66-3.80)
Lymphopaenia not seen	126	12 (10%)	1	1
<b>Pattern of change in proteinuria</b>				
Proteinuria at 6 months regardless of baseline proteinuria status	37	24 (65%)	6.73 (3.34-13.58)	2.63 (1.25-5.54)
Proteinuria at baseline and/or 3 months but not 6 months	95	14 (15%)	1.53 (0.67-3.47)	1.26 (0.62-2.57)
No proteinuria seen	83	8 (10%)	1	1

218 CI: confidence interval; RR: relative risk; ART: antiretroviral therapy.

219 Univariable and multivariable analysis by modified Poisson regression.

220

221 BMI and CD4 count were directly correlated at baseline, 3, and 6 months. TLC and CD4 count  
 222 were moderately positively correlated; while urine protein and CD4 count were inversely  
 223 correlated (see Supplementary Figures 1, 2, and 3 in Additional file 1).

224

225 **Predictors of viral non-suppression at six months among individuals with HIV initiated on**

226 **ART**

227 Only 46 participants (21%) were not virally suppressed at six months. The strongest clinical  
 228 predictors of viral non-suppression in the multivariable analysis were lymphopaenia at six months  
 229 irrespective of baseline lymphocyte status, with 73% of participants with lymphopaenia at six  
 230 months not being suppressed. After adjusting for other factors, lymphopaenia at six months was  
 231 associated with HIV non-suppression {RR = 4.54, 95% CI (2.19-9.39)}. Among participants with

1  
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3 232 a drop in body mass index at six months of 5% or more from baseline, 80% were non-suppressed  
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5 233 {RR = 2.73; 95% CI (1.36-5.47)}. In an alternative analysis, we considered BMI changes of 10%,  
6  
7 234 but only 9 of the non-suppressed participants (20%) had such large decreases. The risk of HIV  
8  
9 235 non-suppression at six months was higher among participants with proteinuria at six months {RR  
10  
11 236 = 2.63; 95% CI (1.25-5.54)}, Table 2. The area under the Receiver Operating Characteristic (ROC)  
12  
13 237 curve for the multivariable model was 0.895 (Fig 2). Baseline HIV stage was not related to HIV  
14  
15 238 non-suppression at six months, {adjusted RR = 1.14, 95% CI (0.63-2.08)} for baseline WHO HIV  
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17 239 clinical stage II and {adjusted RR = 0.82, 95% CI (0.51-1.31)} for advanced baseline WHO HIV  
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19 240 clinical stages (III and IV)}.

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24 241 Using the rounded coefficients of the three variables in a model containing only these variables,  
25  
26 242 which all rounded to 1, we made a “prediction score” with values 0 (n=154, of which 10 were non-  
27  
28 243 suppressed), 1 (n=36, 13 non-suppressed), 2 (n=17, 15 non-suppressed), and 3 (n=8, all non-  
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30 244 suppressed). The median value of this score among the non-suppressed was 1.5 and the first  
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32 245 quartile value was 1. Thus, having any 2 of the risk factors would be a conservative predictor of  
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34 246 non-suppression, and having any one would be less conservative.  
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3 247 **Figure 2. Receiver Operating Characteristic curve assessing a model using BMI decrease,**  
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5 248 **proteinuria, and total lymphocyte counts to predict viral non-suppression among ART naïve**  
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7 249 **individuals with HIV initiated on ART in Dar es Salaam, Tanzania, 2019**  
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17 252 Using the median score among the non-suppressed as a cut-off (equivalent to having any two of  
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19 253 the components), the sensitivity predicting non-suppression was 0.50, and the specificity was 0.99.

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21 254 Only 12% of the study population met this criterion. When we lowered the cut-off scores to the  
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23 255 first quartile value among the non-suppressed (i.e. any one of the components), the sensitivity was  
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25 256 0.78 and the specificity was 0.85, with 28% of the study population meeting this criterion.  
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## 258 Discussion

259 This cohort study recruited ART naïve individuals with HIV from three care and treatment centres  
260 in Dar es Salaam, Tanzania, with the aim of assessing the utility of total lymphocyte count, body  
261 mass index, and proteinuria in predicting ART responses at six months. The intention of this study  
262 is not to replace CD4 cell count testing and HIV viral load monitoring but to assist clinicians when  
263 faced with decision making if these standard monitoring parameters are not easily accessible.  
264 Contrary to earlier studies done when the ART medications were not as effective as the current  
265 ones [12], patient characteristics at ART initiation did not affect the probability of viral non-  
266 suppression at six months, whereas patterns of change and the patient's status at 6 months were  
267 highly predictive.

268 Baseline WHO HIV clinical stage did not help predict HIV non-suppression at six months,  
269 possibly because under the current "Test and Treat" strategy [21], most individuals initiating ART  
270 are in WHO HIV clinical stages I and II (76% of our sample). Current therapy is highly effective  
271 except for a few patients whose disease is so advanced that they die before the medication can  
272 improve their immune status (2 patients in this study). Symptomatic individuals with advanced  
273 HIV will likely adhere to treatment to alleviate their symptoms. Perhaps patients with advanced  
274 disease fear death and therefore are motivated to adhere to ART, with eventual viral suppression.  
275 Advanced HIV disease has been shown to be linked with ART adherence [22]. Some studies,  
276 however, indicate that early HIV stages are linked with high ART adherence and viral suppression  
277 [23].

278 Lymphopaenia at six months, a decrease in body mass index of 5% or more from baseline, and  
279 proteinuria predicted HIV non-suppression at six months. Lymphopaenia at six months was the  
280 strongest predictor for HIV non-suppression at six months. Lymphopaenia at six months predicted

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3 281 HIV non-suppression irrespective of a participant's lymphocyte count (normal or low) before ART  
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5 282 initiation. CD4 cells are a subset of lymphocytes and therefore lymphopaenia could be indicative  
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7 283 of a decline in CD4 cells, as a result of high HIV replication with high viral load signifying viral  
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9 284 non-suppression with consequent CD4 cell destruction. Lymphopaenia was significantly  
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11 285 associated with CD4 <500 cells/mm<sup>3</sup> at all time points. In this study, an increase in total  
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13 286 lymphocyte cell count from lymphopaenia to normal lymphocyte counts from baseline to six  
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15 287 months was significantly associated with an increase in CD4 cell count (Additional file 1). Total  
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17 288 lymphocyte count is sensitive and specific in predicting CD4 cell counts [16,24] though there have  
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19 289 been contradictory reports [25]. The assessment of total lymphocyte counts among patients on  
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21 290 ART, therefore, could serve as an alternative, especially in settings with limited availability of  
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23 291 CD4 cell count measurement. A drop in total lymphocyte count in such a setting can alert a  
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25 292 clinician to the likelihood of immunological failure. A drop in lymphocytes could also signal the  
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27 293 possibility of immunological non responders, who will need primary and secondary prophylaxis  
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29 294 for opportunistic infection.

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31 295 Weight loss with consequent BMI drop of 5% or more at six months while on ART from weight  
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33 296 prior to ART initiation, predicts HIV non-suppression, though HIV non-suppression was not  
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35 297 associated with being underweight prior to ART initiation, perhaps because of the low prevalence  
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37 298 of underweight leading to low power. In this study, sustained weight gain was significantly  
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39 299 associated with viral suppression and sustained weight loss was associated with viral non-  
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41 300 suppression at six months of ART. An increase in weight and hence BMI may be a sign of immune  
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43 301 status improvement signalling a return to health [26,27] and improved survival [28], while a  
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45 302 decrease in weight and hence BMI may be a sign of HIV progression or decline in CD4 cell counts  
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47 303 [5,11,29]. Weight loss may be due to HIV itself, opportunistic infections, or HIV-associated

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3 304 tumours. Failure to gain weight has been associated with efavirenz toxicity over time as was  
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5 305 observed in a study in South Africa [30]. Weight loss in both ART naïve and exposed patients has  
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7 306 been associated with increased morbidity and mortality [31,32]. A study in England observed that  
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9 307 each log<sub>10</sub> increase in HIV viral load was associated with a 0.92 kg decrease in body weight.  
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11 308 However, a decrease in viral load was not significantly associated with weight gain, contrary to  
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13 309 our study [33]. Since weight changes correlate with the virological response, losing weight should  
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15 310 be viewed as an alarming sign of HIV viral non suppression from any cause. Monitoring of weight  
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17 311 and body mass index prior to ART initiation and during follow up is a valuable inexpensive way  
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19 312 of identifying individuals with possible viral non suppression. In an alternative analysis, we  
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21 313 considered BMI changes of 10%, but only 9 of the non-suppressed participants (20%) had such  
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23 314 large decreases, making the 10% decrease not useful as a cut-off in our situation.  
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29 315 Half of the ART-naïve study participants had proteinuria, similar to a report from Zimbabwe [34].  
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31 316 The presence of proteinuria was associated with HIV non-suppression. Proteinuria at six months  
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33 317 was a strong predictor of HIV non-suppression. Proteinuria in individuals with HIV is attributed  
34  
35 318 to a direct effect of HIV on the glomerular and tubular epithelial cells with the progression of HIV  
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37 319 disease to AIDS, nephrotoxicity from ART, the progression of chronic kidney disease and death  
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39 320 [14,35] The higher the viral load, the greater the damage to the kidney [36]. We observed a  
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41 321 significant proportion of participants with proteinuria of 2+ or above in WHO HIV clinical stage  
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43 322 IV. This underscores the fact that, as HIV disease advances, the greater the damage to the kidneys  
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45 323 as evidenced by increasing proteinuria. Therefore, routine screening for renal disease may serve  
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47 324 not only as a follow-up of renal disease progression but also for HIV treatment response  
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49 325 monitoring.  
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3 326 The presence of proteinuria, lymphopaenia, and a drop in BMI of 5% are relatively simple  
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5 327 parameters to monitor among people living with HIV on ART especially in a setting where viral  
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7 328 load monitoring is a challenge. The presence of any of these parameters should alert a clinician on  
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10 329 the possibility of viral non-response and review adherence issues including individualized  
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12 330 enhanced adherence counselling and subsequent treatment options.

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15 331 Our findings require validation in a study with a larger sample size. Our small sample may have  
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17 332 constrained some predictors of viral non-suppression. Similar studies conducted in different  
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19 333 locations are also needed since local conditions and treatment standards may influence some  
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21 334 observed patterns, both in prevalence and effect. Furthermore, use of new antiviral drugs and  
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23 335 changes in patient characteristics at presentation may change our estimates, and possibly the  
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25 336 important predictor variables. We recommend further studies with extended follow up of patients  
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27 337 beyond six months to monitor further change in lymphopaenia, proteinuria and drop in BMI of 5%  
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29 338 or more especially for individuals maintained on the same regimen after enhanced adherence  
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31 339 counselling. We recommend further studies to examine the relationship between virological  
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33 340 response and anaemia as well as opportunistic infections and AIDS associated malignancies  
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35 341 especially now that ART is initiated early.

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38 342 One strength of our study is the cohort design with complete follow up data at three and six months  
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41 343 for 98% of the enrolled participants. Although our scoring system is crude, it is easy to compute  
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43 344 and is likely to be valid for a wide variety of situations, whereas a score based on more precise  
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45 345 computations would at best work only in our location.

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54 347 **Conclusion**

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3 348 A drop in BMI by more than 5%, persistent lymphopaenia or decrease in total lymphocyte count  
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5 349 to lymphopaenia, and proteinuria at six months are associated with HIV non-suppression at 6  
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7  
8 350 months after ART initiation. Scores based on these parameters are easy to use and can serve as  
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10 351 alternatives to CD4 cell counts and viral load assessment in facilities with scarcity.  
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### 13 352 **List of abbreviations**

14  
15  
16 353 AIDS: Acquired immunodeficiency syndrome  
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18  
19 354 ART: Antiretroviral therapy  
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21  
22 355 BMI: Body mass index  
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25 356 CD4: Cluster of differentiation 4  
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28 357 HIV: Human immunodeficiency virus  
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31 358 TLC: Total lymphocyte counts  
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34 359 WHO: World Health Organization  
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52

### 53 366 **Author Contributions**

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57



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2  
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4  
5 368 BT and EH; Manuscript writing: LJ, PM, BT and EH. All the authors gave final approval of the  
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8 369 manuscript.  
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23  
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27  
28 376 **Patient consent for publication**

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31 377 Not applicable.  
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33  
34 378 **Ethics approval**

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38  
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40  
41 381 study was obtained from Temeke Municipal Hospital administration. Participants were enrolled  
42  
43 382 after providing written informed consent. The confidentiality of patient information was ensured.  
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45  
46 383 Participants without viral suppression at the 6<sup>th</sup> month of follow up were managed according to  
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48 384 Tanzania National Guidelines for management of HIV and AIDS.  
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51 385 **Data availability statement**  
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3 386 The dataset analysed during the current study is available upon reasonable request to the  
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5 387 corresponding author.  
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### 14 391 **Ethics Statement**

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16 392 Muhimbili University of Health and Allied Sciences Institutional Review Board with reference  
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18 393 number DA287/298/01A/  
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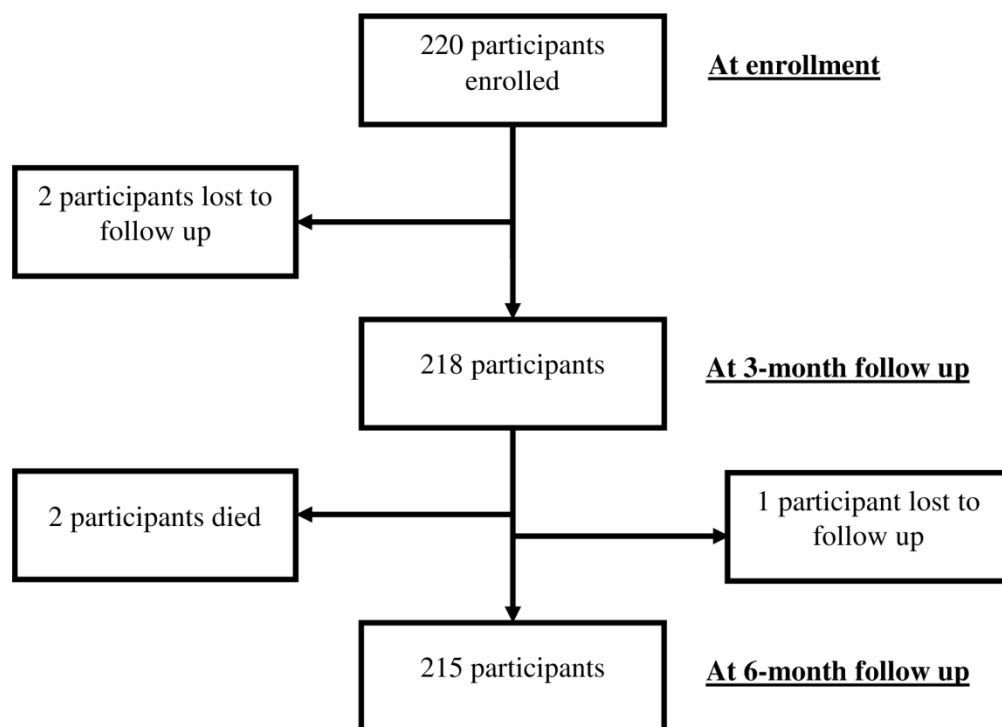


Figure 1. Consort diagram.

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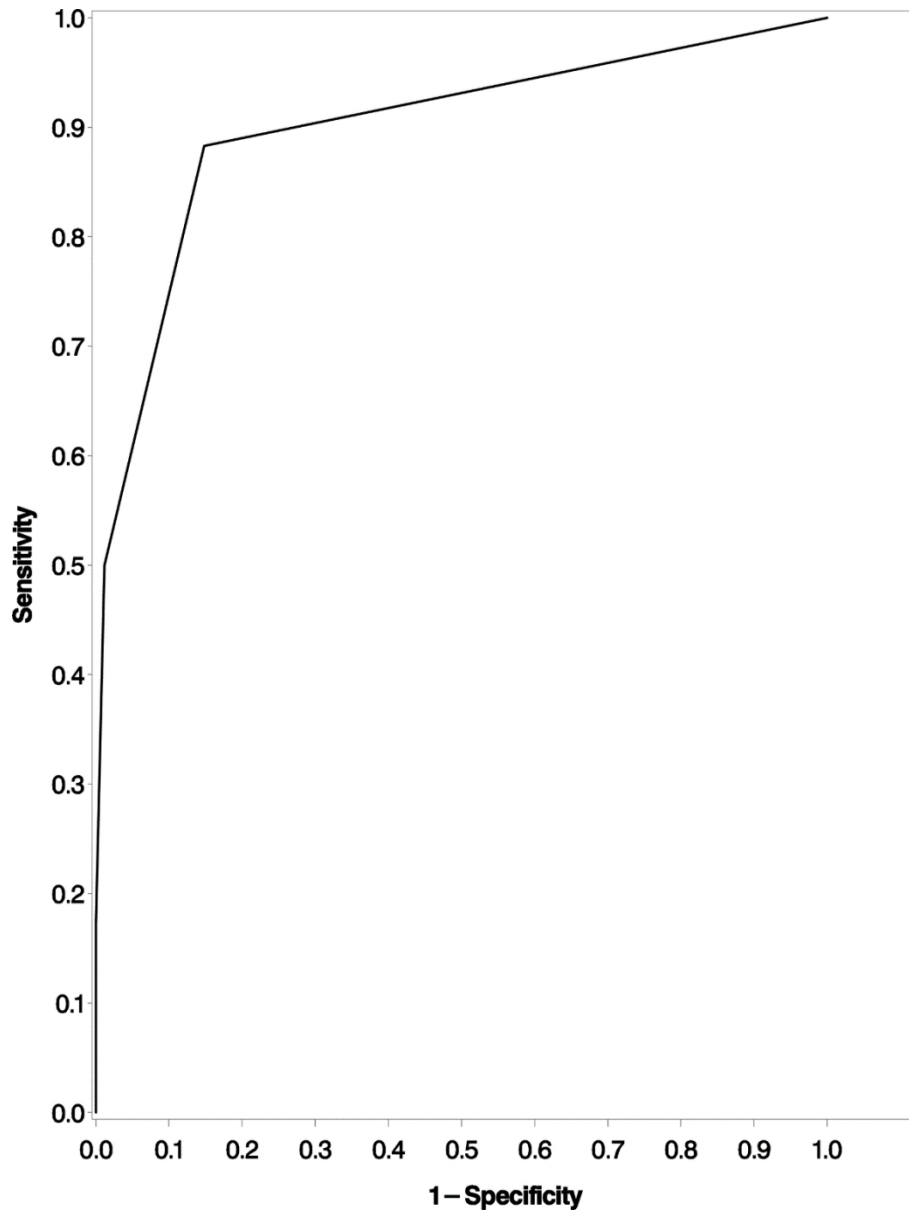
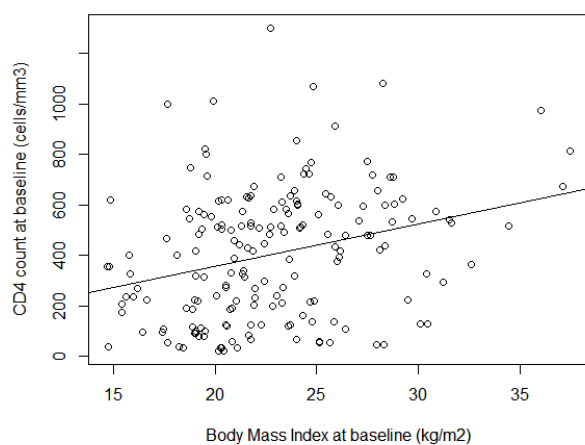


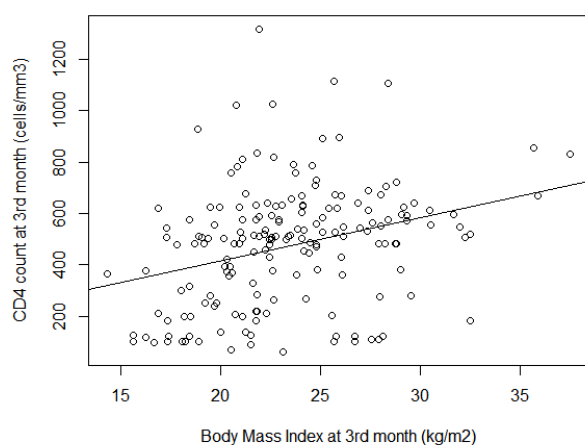
Figure 2. Receiver Operating Characteristic curve assessing a model using BMI decrease, proteinuria, and total lymphocyte counts to predict viral non-suppression among HIV-infected individuals initiated on ART in Dar es Salaam, Tanzania, 2019

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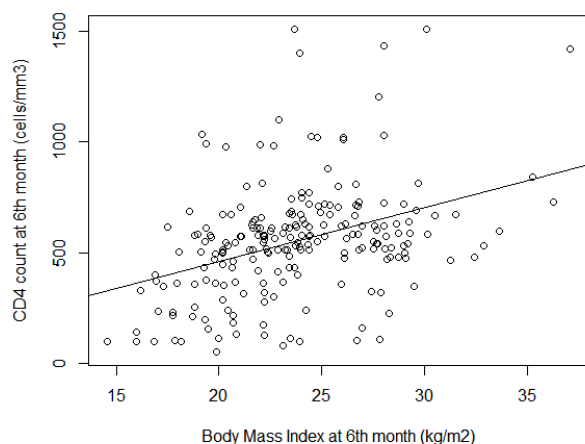
## Supplementary Figure 1. Scatter plots of BMI and CD4 counts



rho 0.287, p <0.0001

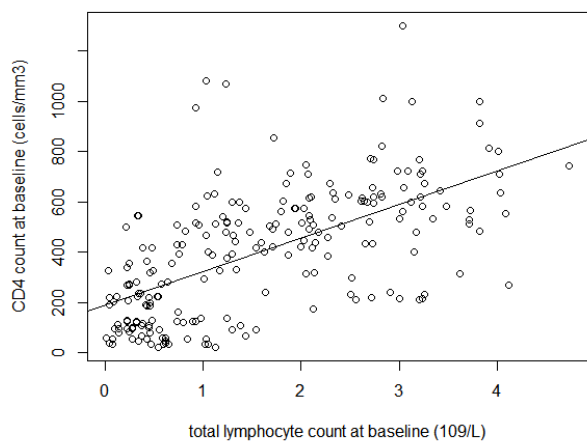


rho 0.305, p <0.0001

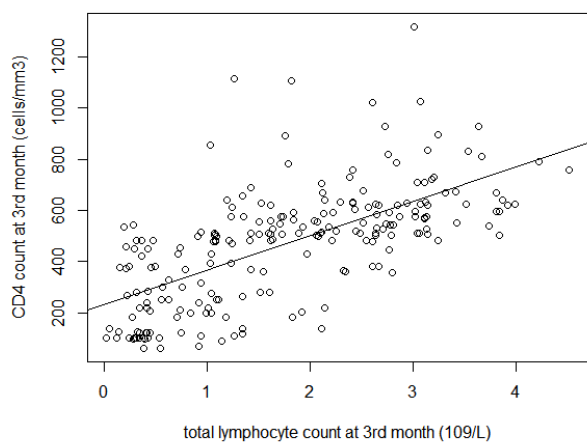


rho 0.373, p <0.0001

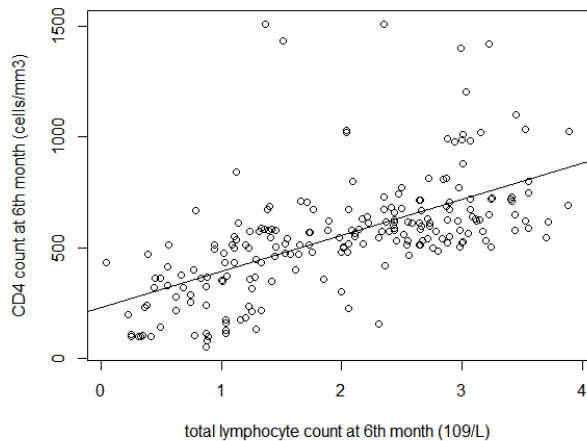
Supplementary Figure 2. Scatter plots of total lymphocyte count and CD4 count



rho 0.613, p <0.0001

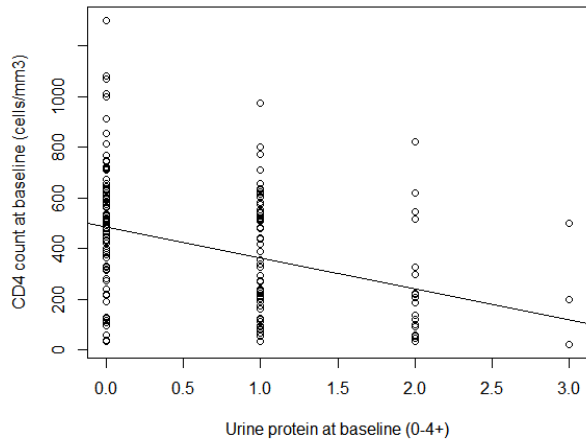


rho 0.650, p <0.0001

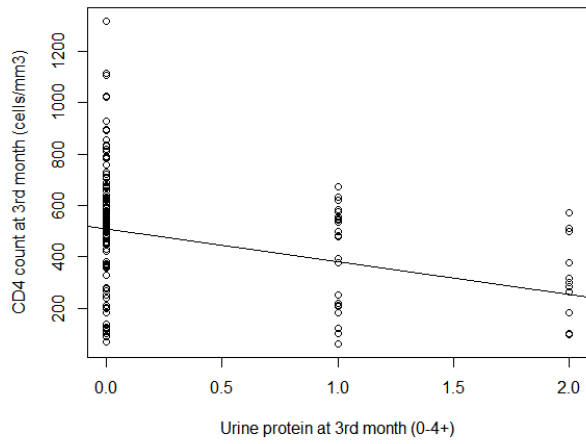


rho 0.602, p <0.0001

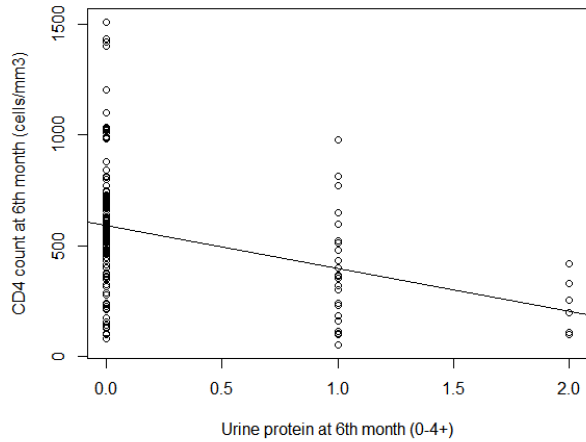
Supplementary Figure 3. Scatter plots of urine protein and CD4 count



rho -0.364, p <0.0001



rho -0.334, p <0.0001



rho -0.372, p <0.0001

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

			Page
		Reporting Item	Number
<b>Title and abstract</b>			
Title	<a href="#">#1a</a>	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	<a href="#">#1b</a>	Provide in the abstract an informative and balanced summary	3

of what was done and what was found

## Introduction

Background / [#2](#) Explain the scientific background and rationale for the 6  
rationale investigation being reported

Objectives [#3](#) State specific objectives, including any prespecified 7  
hypotheses

## Methods

Study design [#4](#) Present key elements of study design early in the paper 8

Setting [#5](#) Describe the setting, locations, and relevant dates, including 8-10  
periods of recruitment, exposure, follow-up, and data collection

Eligibility criteria [#6a](#) Give the eligibility criteria, and the sources and methods of 8-10  
selection of participants. Describe methods of follow-up.

Eligibility criteria [#6b](#) For matched studies, give matching criteria and number of -  
exposed and unexposed

Variables [#7](#) Clearly define all outcomes, exposures, predictors, potential 9,10  
confounders, and effect modifiers. Give diagnostic criteria, if  
applicable

Data sources / [#8](#) For each variable of interest give sources of data and details of 8-10  
measurement methods of assessment (measurement). Describe  
comparability of assessment methods if there is more than one  
group. Give information separately for for exposed and  
unexposed groups if applicable.

1	Bias	<a href="#">#9</a>	Describe any efforts to address potential sources of bias	
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4	Study size	<a href="#">#10</a>	Explain how the study size was arrived at	8
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7	Quantitative	<a href="#">#11</a>	Explain how quantitative variables were handled in the	9-11
8	variables		analyses. If applicable, describe which groupings were chosen,	
9			and why	
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15	Statistical	<a href="#">#12a</a>	Describe all statistical methods, including those used to control	
16	methods		for confounding	
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23	Statistical	<a href="#">#12b</a>	Describe any methods used to examine subgroups and	10, 11
24	methods		interactions	
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29	Statistical	<a href="#">#12c</a>	Explain how missing data were addressed	12
30	methods			
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34	Statistical	<a href="#">#12d</a>	If applicable, explain how loss to follow-up was addressed	-
35	methods			
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39	Statistical	<a href="#">#12e</a>	Describe any sensitivity analyses	
40	methods			
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48	<b>Results</b>			
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51	Participants	<a href="#">#13a</a>	Report numbers of individuals at each stage of study—eg	12
52			numbers potentially eligible, examined for eligibility, confirmed	(figure 1)
53			eligible, included in the study, completing follow-up, and	
54			analysed. Give information separately for for exposed and	
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unexposed groups if applicable.

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4	Participants	<a href="#">#13b</a>	Give reasons for non-participation at each stage
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9	Participants	<a href="#">#13c</a>	Consider use of a flow diagram
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12	12 (figure 1)		
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15	Descriptive data	<a href="#">#14a</a>	Give characteristics of study participants (eg demographic,
16			clinical, social) and information on exposures and potential
17			confounders. Give information separately for exposed and
18			unexposed groups if applicable.
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25	Descriptive data	<a href="#">#14b</a>	Indicate number of participants with missing data for each
26			variable of interest
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33	Descriptive data	<a href="#">#14c</a>	Summarise follow-up time (eg, average and total amount)
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40	Outcome data	<a href="#">#15</a>	Report numbers of outcome events or summary measures
41			over time. Give information separately for exposed and
42			unexposed groups if applicable.
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50	Main results	<a href="#">#16a</a>	Give unadjusted estimates and, if applicable, confounder-
51			adjusted estimates and their precision (eg, 95% confidence
52			interval). Make clear which confounders were adjusted for and
53			why they were included
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1	Main results	<a href="#">#16b</a>	Report category boundaries when continuous variables were	12-15
2			categorized	
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6	Main results	<a href="#">#16c</a>	If relevant, consider translating estimates of relative risk into	
7			absolute risk for a meaningful time period	
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15	Other analyses	<a href="#">#17</a>	Report other analyses done—eg analyses of subgroups and	16
16			interactions, and sensitivity analyses	
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20	<b>Discussion</b>			
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23	Key results	<a href="#">#18</a>	Summarise key results with reference to study objectives	20
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26	Limitations	<a href="#">#19</a>	Discuss limitations of the study, taking into account sources of	5
27			potential bias or imprecision. Discuss both direction and	
28			magnitude of any potential bias.	
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34	Interpretation	<a href="#">#20</a>	Give a cautious overall interpretation considering objectives,	18-20
35			limitations, multiplicity of analyses, results from similar studies,	
36			and other relevant evidence.	
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42	Generalisability	<a href="#">#21</a>	Discuss the generalisability (external validity) of the study	20
43			results	
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47	<b>Other Information</b>			
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50	Funding	<a href="#">#22</a>	Give the source of funding and the role of the funders for the	22
51			present study and, if applicable, for the original study on which	
52			the present article is based	
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3 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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