Suboptimal Immune Recovery Despite Suppressive Antiretroviral Therapy in Africa

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Background

- Suboptimal immune recovery, despite suppressive antiretroviral therapy (ART), has been associated with an increased risk of HIV-related illnesses.

Objectives

- To assess the occurrence of suboptimal immune recovery in sub-Saharan Africa, using clinically relevant CD4 cell count thresholds
- To identify factors associated with failure of immune recovery
- To assess the incidence of TB, AIDS and death and its association with Immune recovery during long term ART.

Table 1. Clinically relevant CD4 cell count categories

>500 cells/µl	No immunosuppression
350-499 cells/µl	Mild immunosuppression
200-349 cells/µl	Advanced immunosuppression
<200 cells/µl	Severe immunosuppression

Study Participants

1581 HIV positive participants from Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe enrolled in the Pan-African Studies to Evaluate Resistance (PASER) adult cohort, were eligible for this analysis.

Inclusion criteria:

- Initiation of first-line non-nucleoside-reverse-transcriptase-inhibitor-based ART
- Undetectable plasma viral load (<50cps/mL) after 12 months and thereafter

Figure 1. PASER sites

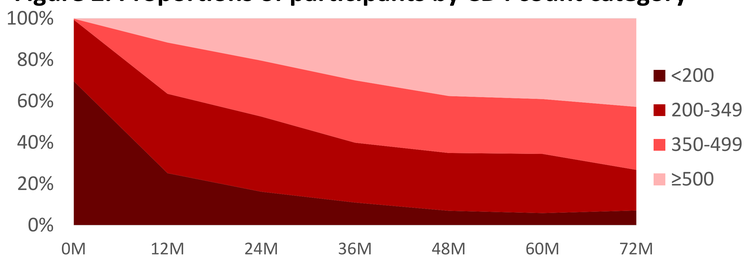


Data analysis

- Suboptimal immune recovery was defined by proportions of participants by CD4 count strata over time.
- Incidence rates of TB, AIDS and death by time updated CD4 count strata <200, 200-349, 350-499 and ≥500 cells/µl was calculated using a time to event analysis.
- Multivariable Cox regression analysis was done to identify baseline factors associated with suboptimal immune recovery. Clustering of observations within countries was taken into account. Multiple imputations was used to account for missing baseline variables.

Proportions of participants with suboptimal immune recovery

Figure 2. Proportions of participants by CD4 count category



- **At ART initiation, 70% of the participants had CD4 cell counts of <200 cells/µL, and 99% <350cells/µL.**
- **After 6 years of suppressive ART, 57.6% had CD4 cell counts of <500cells/µL and 26.8% <350 cells/µL.**

Incidence rate of HIV-related events by time updated CD4 count outcome strata

Table 2. Incidence rates per 100person-years of TB, AIDS and death by time-updated CD4 count outcome strata

HIV related event	CD4 <200cells/µL Rate (95% CI)	CD4 200-349 cells/µL Rate (95% CI)	CD4 350-499 cells/µL Rate (95% CI)	CD4 ≥500cells/µL Rate (95% CI)
TB	3.32(2.40 - 4.58)	0.85(0.50 - 1.43)	0.40(0.17 - 0.95)	0.25(0.08 - 0.76)
AIDS	4.21(3.17 - 5.61)	1.33(0.88 - 2.02)	0.48(0.21 - 1.06)	0.41(0.17 - 0.99)
Death	0.72(0.36 - 1.43)	0.54(0.28 - 1.05)	0.08(0.01 - 0.56)	0.66(0.33 - 1.31)

- **Persons with CD4<500 cells/µL had an increased risk of TB and AIDS.**
- **Mortality rates were similar across CD4 strata, with an overall mortality rate of 0.50 (0.34 – 0.73) events/100PYR**

Discussion

- Suboptimal immune recovery is frequent in African adults: 57,6% do not reach the CD4>500 cells/µL threshold after 6 years of ART.
- Persons with CD4<500 had an increased risk of TB and AIDS but not death, compared to CD4<200.
- The main factors associated with suboptimal immune recovery were: Male sex, older age, low CD4 cell count at initiation of ART
- Close laboratory and clinical monitoring is required for those with CD4 cell counts of <500 cells/µL and those who have risk factors of suboptimal immune recovery.
- The study findings highlights the importance of early HIV diagnosis and ART initiation in accordance with the latest international guidelines.

Factors associated with suboptimal immune recovery

Table 3. Patient characteristics independently associated with suboptimal immune recovery during ART

	CD4 <200 cells/µL		CD4 <350 cells/µL		CD4 <500 cells/µL	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Male sex	1.29 (1.13 - 1.46)	0.000	1.32 (1.03 - 1.70)	0.030	1.71 (1.27 - 2.30)	0.000
age						
18-29	1.00		1.00		1.00	
30-39	1.06 (0.76 - 1.47)	0.751	1.22 (0.95 - 1.55)	0.118	1.50 (1.20 - 1.87)	0.000
40-49	1.02 (0.79 - 1.31)	0.885	1.19 (0.94 - 1.51)	0.147	1.47 (1.24 - 1.73)	0.000
≥50	1.32 (1.01 - 1.74)	0.045	1.58 (1.22 - 2.05)	0.001	2.64 (1.68 - 4.16)	0.000
CD4 count baseline (cells/µL)						
<100	2.35 (1.99 - 2.77)	0.000	5.05 (4.52 - 5.64)	0.000	4.90 (3.53 - 6.81)	0.000
100-199	1.00		2.64 (2.18 - 3.19)	0.000	2.49 (1.95 - 3.19)	0.000
≥200			1.00		1.00	
BMI baseline (kg/m²)						
<18	1.06 (0.90 - 1.26)	0.482	0.95 (0.76 - 1.18)	0.624	0.80 (0.55 - 1.15)	0.220
18-25	1.00		1.00		1.00	
>25	0.77 (0.65 - 0.90)	0.001	0.83 (0.73 - 0.94)	0.004	0.74 (0.62 - 0.89)	0.001
HIV-1 subtype						
C	1.00		1.00		1.00	
A	1.11 (0.80 - 1.56)	0.525	1.15 (1.01 - 1.32)	0.040	1.24 (0.90 - 1.71)	0.191
D	1.09 (0.78 - 1.52)	0.606	1.22 (0.95 - 1.56)	0.121	1.25 (0.94 - 1.65)	0.122
other	0.72 (0.45 - 1.14)	0.162	0.89 (0.69 - 1.15)	0.391	1.05 (0.84 - 1.32)	0.647
ART regimen						
TDF/(X)TC*/EFV	1.00		1.00		1.00	
TDF/(X)TC*/NVP	0.85 (0.72 - 0.99)	0.038	0.92 (0.77 - 1.09)	0.334	0.98 (0.82 - 1.17)	0.839
d4T/3TC/EFV	1.40 (0.98 - 2.01)	0.064	0.94 (0.66 - 1.35)	0.740	0.87 (0.65 - 1.16)	0.339
d4T/3TC/NVP	1.14 (0.77 - 1.68)	0.509	0.92 (0.67 - 1.27)	0.630	1.53 (1.19 - 1.97)	0.001
AZT/3TC/EFV	1.25 (1.07 - 1.47)	0.004	1.21 (1.03 - 1.42)	0.022	1.26 (1.01 - 1.57)	0.040
AZT/3TC/NVP	1.02 (0.70 - 1.47)	0.932	0.97 (0.76 - 1.25)	0.820	1.11 (0.92 - 1.35)	0.273
ABC/3TC/EFV	0.69 (0.56 - 0.86)	0.001	0.97 (0.70 - 1.35)	0.849	1.79 (1.20 - 2.66)	0.004
ABC/3TC/NVP	0.63 (0.23 - 1.75)	0.376	0.54 (0.21 - 1.41)	0.208	0.95 (0.37 - 2.48)	0.924

*** (X)TC= 3TC or FTC**

- **Male sex, older age, low baseline CD4, AZT/3TC/EFV was associated with a higher risk of suboptimal immune recovery <200, <350 and <500.**
- **High BMI was associated with lower risk of suboptimal immune recovery <200, <350 and <500.**
- **Additionally, TDF/(X)TC/NVP and ABC/3TC/EFV were associated with a lower risk of suboptimal immune recovery <200, HIV-1 subtype A was associated with a higher risk of suboptimal immune recovery <350, d4T/3TC/NVP and ABC/3TC/EFV was associated with a higher risk of suboptimal immune recovery <500.**

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