Implications of Poor CD4 Recovery during HIV Suppressive ART in sub-Saharan Africa

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Keywords **antiretroviral treatment, resource-limited setting, poor CD4 recovery, HIV-1**

background

- Achieving undetectable plasma viral load (VL) on antiretroviral therapy (ART) is not always accompanied by the recovery of CD4 count. This study evaluates determinants, clinical outcomes and time trends of poor CD4 recovery in patients receiving suppressive ART in the Pan-African Studies to Evaluate Resistance Monitoring (PASER-M) cohort.

methodology

- In 2585 patients with pre-ART CD4<200 cells/μL and VL<50 RNA c/mL, poor CD4 recovery was defined as CD4 count <200 and a CD4 gain from baseline <100 cells/μL at month 12, and CD4 count <350 and CD4 gain from baseline <100 cells/μL at month 24. Determinants of poor CD4 recovery were assessed using logistic regression. Clinical outcome (mortality) beyond 12 months was assessed in groups of patient with poor versus good CD4 recovery at month 12, using logistic regression and Kaplan-Meier analysis. Time trends in the proportions of poor CD4 recovery were examined in relation to (change in) the predictive capacity of CD4 count to identify virological failure using WHO-recommended immunological criteria, at month 12, 24 and 36.

results

Determinants of poor CD4 recovery in virologically suppressed patients after 12 & 24 months on ART (Table 1 & 2)

- After 12 months of follow-up, 1,946 (75.3%) patients were still alive, retained in care, and on first-line ART. Of these patients, 1,361 (70.0%) had both a viral load < 50 cps/ml and CD4 test results available. A total of 212 (15.6%) out of 1361 patients had poor CD4 recovery. Risk factors of poor CD4 recovery at month 12 were older age ≥40 (OR=2.42, 95%CI1.47-3.98) and lower pre-ART CD4 count per 50 cells/μL stage (OR=0.65, 95%CI 0.59-0.72). After 24 months of follow up, 1,804 (92.3%) patients were still alive, retained in care and on first line ART. Of these patients, 1,283 (71.1%) had a persistently undetectable viral load at month 12 and 24. CD4 test results were available of 1,003 (78.2%) patients. After 24 months, 199 (19.8%) out of 1003 patients presented with poor CD4 recovery. Risk factors of poor CD4 recovery at month 24 were male sex (OR=1.61, 95%CI1.12-2.31), AIDS at ART initiation (OR=0.46, CI 95%0.25-0.84), and poor CD4 recovery at month 12 (OR=9.45, CI95% 6.33-14.10). Determinants of persistent poor CD4 recovery, at both month 12 and 24, were older age (OR=3.90, CI95%1.45-10.49), lower pre-ART CD4 count (OR=0.74, CI95%0.63-0.87) and AIDS at ART initiation (OR=0.36, CI95%0.15-0.89).

HIV-related mortality of virologically-suppressed patients with poor CD4 recovery at month 12 (Figure 1)

- Of the 212 (15.6%) participants with PIR at month 12 (table 2), 6 (2.8%) experienced HIV-related mortality as compared to 10 of the 1,149 participants with a good CD4 recovery (0.9%). Poor CD4 recovery at month 12 was associated with a significantly higher risk of HIV-related mortality between month 12 and 24 (OR=3.78, CI95%1.26-11.41). A Kaplan-Meier curve was calculated; log rank results show a higher risk to die for participants in the group <200cells/μL, as compared to the group of patients with a CD4 count between 200-350 cells/μL (p=0.059). In addition, participants in the group <200cells/μL show a higher risk to die as compared to the groups >350cells/μL (p=0.034). Patients with a CD4 <200 cells/μL at month 12 showed an incidence density of 10 per 1000 person years, while patients with a CD4 >200 cells/μL at month 12 showed an incidence density of 2.9 per 1000 patient years (95%CI 0.74-21.5)

Impact on the predictive capacity of immunological criteria on treatment response (gure 2)

- Proportions of poor CD4 recovery remained stable among virologically suppressed patients throughout the follow-up period (12.8 % at month 12, 19.8% at month 24 and 16.1% at month 36). In settings where immunological criteria are used to identify treatment failure, unchanging proportion of poor CD4 recovery over time translates into stable proportions of false positives (8.2% at month 12, 5.4% at month 24, and 10.2% at month 36). This contributes in part to the persistently low predictive capacity of WHO-defined immunological criteria on virological failure throughout the observation period (PPV= 16%, 34% and 37% at month 12, 24 and 36).

conclusions

- **The public health approach to ART should intensify strategies for achieving immune recovery to avoid an enduring high risk of mortality despite viral suppression in certain sub-groups of patients. These strategies should include the timely identi cation and treatment of ART-eligible patients prior to severe CD4 decline as well as treatment support interventions targeting male and older patients.**
- **CD4 count has little added value to VL monitoring in identifying virological failure to ART, with no tendency to improve over time. CD4 count may however carry important information on HIV-related mortality during suppressive ART in a sub-group of patients not achieving optimal reconstitution of their CD4 count. Hence, CD4 enumeration remains important also in settings where VL testing is available. In the rst two years of ART, CD4 count monitoring could allow the identi cation of virologically-suppressed patients with higher risk of mortality. Beyond two years of ART, CD4 count could be phased out in virologically and immunologically stable patients and continued in patients with poor CD4 recovery, in order to support the prevention of opportunistic infections.**

Table 1 patient characteristics at ART initiation in the PASER M cohort

	Total (n=2,585) N (%)	Poor CD4 recovery at month 12 (n=212)	Good CD4 recovery at month 12 (n=1,149)	p-value	Poor CD4 recovery at month 24 (N=199)	Good CD4 recovery at month 24 (N=804)	p-value
Sex (female)	1486 (57.5)	111 (52.4)	697 (60.7)	0.024	96 (48.2)	512 (63.7)	<0.0001
Age (SD)	37.9 (8.9)	39.9 (8.8)	37.9 (8.9)	0.023	40.4 (9.7)	37.8 (8.5)	<0.0001
Calendar year of initiation							
2007	610 (23.6)	42 (19.8)	254 (22.1)	0.419	37 (18.6)	181 (22.5)	0.438
2008	1599 (61.9)	141 (66.5)	710 (61.8)		126 (63.3)	474 (59.0)	
2009	376 (14.1)	29 (13.7)	185 (16.1)		36 (18.1)	149 (18.5)	
Country							
Zambia	554 (21.4)	232 (20.2)	37 (17.5)	0.025	34 (17.1)	154 (19.2)	0.107
South Africa	596 (23.1)	201 (17.5)	23 (10.9)		21 (10.6)	122 (15.2)	
Uganda	603 (23.3)	324 (28.2)	69 (32.6)		67 (33.7)	23 (28.6)	
Kenya	418 (16.2)	162 (14.1)	41 (19.3)		28 (14.1)	98 (12.2)	
Zimbabwe	212 (8.2)	142 (12.4)	20 (9.4)		33 (16.6)	101 (12.6)	
Nigeria	202 (7.8)	88 (7.7)	22 (10.4)		16 (8.0)	99 (12.3)	
WHO clinical stage							
1 or 2	1201 (39.5)	82 (38.7)	463 (40.8)	0.395	95 (47.7)	331 (41.2)	0.104
3	1142 (44.2)	99 (46.7)	499 (43.4)		85 (42.7)	346 (43.0)	
4	422 (16.3)	31 (14.6)	181 (15.8)		19 (9.6)	127 (15.8)	
Type of initial NRTI-backbone [a]							
Zidovudine based	960 (37.1)	110 (51.9)	472 (41.1)	0.029	99 (49.8)	353 (43.9)	0.119
Stavudine based	694 (26.9)	37 (17.5)	244 (21.2)		24 (12.2)	150 (18.7)	
Tenofovir based	864 (33.4)	63 (29.7)	410 (35.7)		73 (36.7)	282 (35.1)	
Abacavir based	67 (2.6)	2 (0.9)	23 (2.0)		3 (1.5)	19 (2.4)	
Type of initial NNRTI							
Efavirenz	1537 (59.5)	101 (47.6)	658 (47.6)	0.010	95 (47.7)	412 (51.2)	0.376
Nevirapine	1048 (40.5)	111 (52.4)	491 (42.7)		104 (52.3)	392 (48.8)	
CD4 cell count cells/µL (IQR)	136.8 (62-202)	129.3 (99-170)	143.5 (249-433)	<0.0001	160 (102-214)	146 (73-211)	0.069
HIV RNA load log10 RNA copies/ml (IQR)	4.9 (4.4-5.6)	4.9 (4.3-5.6)	4.9 (4.3-5.6)	0.706	4.8 (4.2-5.4)	4.9 (4.4-5.6)	0.048
Haemoglobin (IQR)	11.5 (10-12.9)	11.5 (9.9-12.8)	11.6 (10.1-13)	0.236	11.8 (10.5-13.3)	11.5 (9.9-13.0)	0.386

[a] *plus Lamivudine or Emtricitabine*

Figure 2 PASER sites

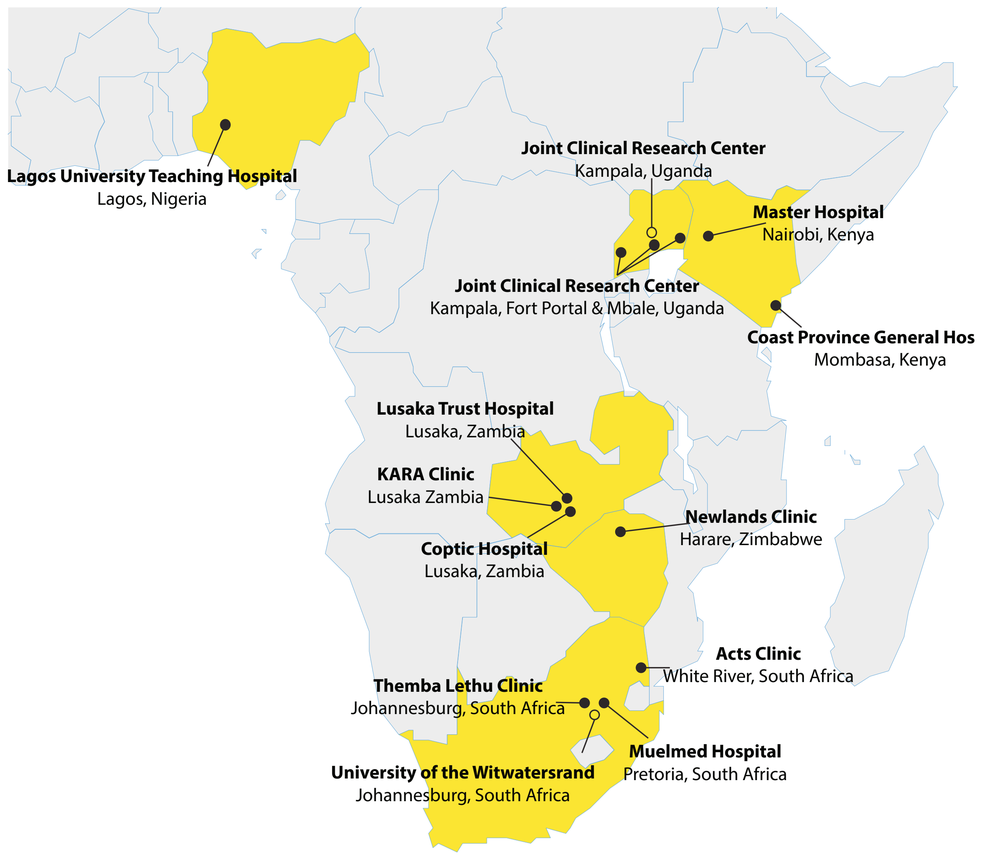
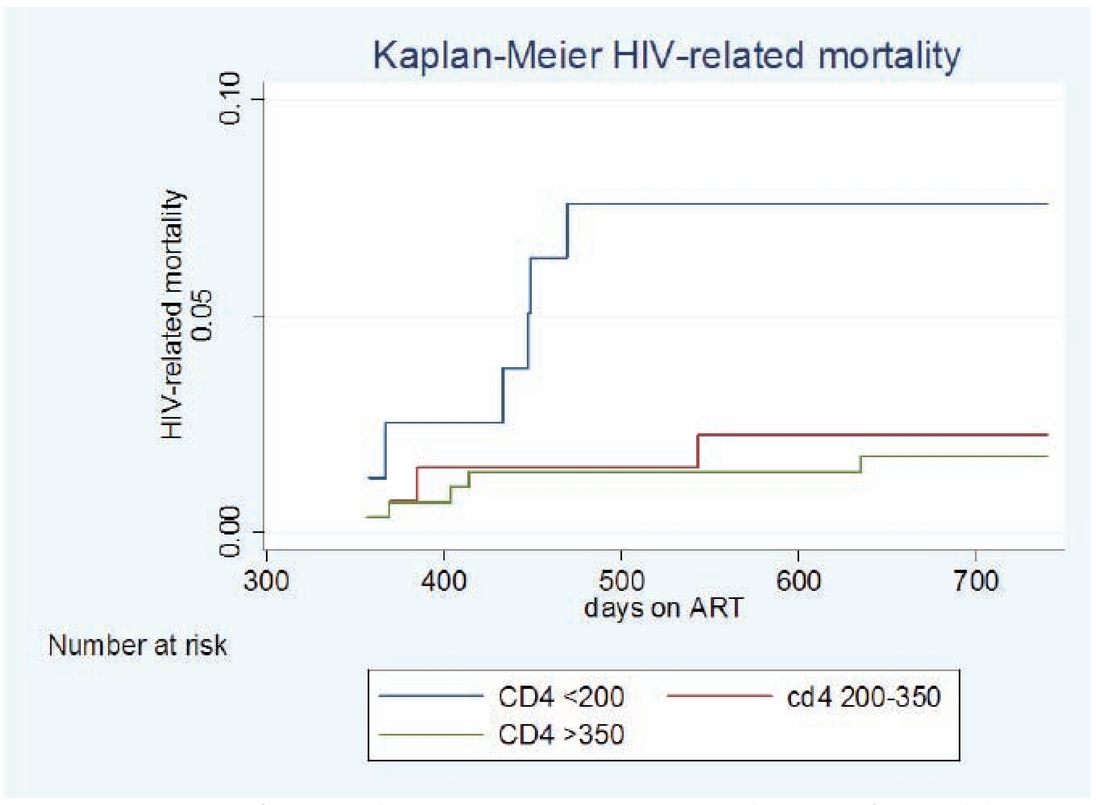


Table 2 Determinants for poor CD4 recovery in patients with viral suppression at month 12 & 24

	MONTH 12 Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value	MONTH 24 Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Sex								
Female	Reference		Reference		Reference		Reference	
Male	1.41 (1.04-1.90)	0.023	1.19 (0.86-1.63)	0.293	1.76 (1.26-2.46)	0.001	1.61 (1.12-2.31)	0.010#
Age								
18-29	Reference		Reference		Reference		Reference	
30-39	1.64 (1.01-2.67)	0.046#	1.60 (0.96-2.64)	0.071	1.19 (0.70-2.03)	0.513	0.83 (0.47-1.48)	0.535
≥40	2.13 (1.32-3.43)	0.002#	2.42 (1.47-3.98)	<0.001#	1.79 (1.07-2.90)	0.025	1.12 (0.64-1.97)	0.683
CD4 cell count at baseline (per 50 cells/µL increase)	0.67 (60.7-0.74)	<0.001#	0.65 (0.59-0.72)	<0.001#	1.10 (1.00-1.21)	0.140	-	-
NRTI-backbone [a]								
TDF	Reference		Reference		Reference		-	-
ABC	0.59 (0.13-2.65)	0.489	0.47 (0.10-2.16)	0.330	0.23 (0.03-1.79)	0.159	-	-
D4T	1.06 (0.64-1.76)	0.817	0.78 (0.45-1.28)	0.300	0.62 (0.35-1.12)	0.111	-	-
ZDV	1.46 (1.00-2.11)	0.048	1.33 (0.88-2.01)	0.170	0.95 (0.63-1.43)	0.812	-	-
Initial type of NNRTI								
Efavirenz	Reference		Reference		Reference		-	-
Nevirapine	1.40 (1.01-1.94)	0.042	1.41 (0.98-2.03)	0.067	1.18 (0.82-1.71)	0.374	-	-
AIDS at initiation								
No	Reference		-	-	Reference		Reference	
Yes	0.91 (0.60-1.38)	0.653	-	-	0.54 (0.31-0.94)	0.029	0.46 (0.25-0.84)	0.012#
Poor CD4 recovery at month 12								
No	-	-	-	-	Reference		Reference	
Yes	-	-	-	-	9.54 (6.42-14.18)	<0.001	9.45 (6.33-14.10)	<0.001#

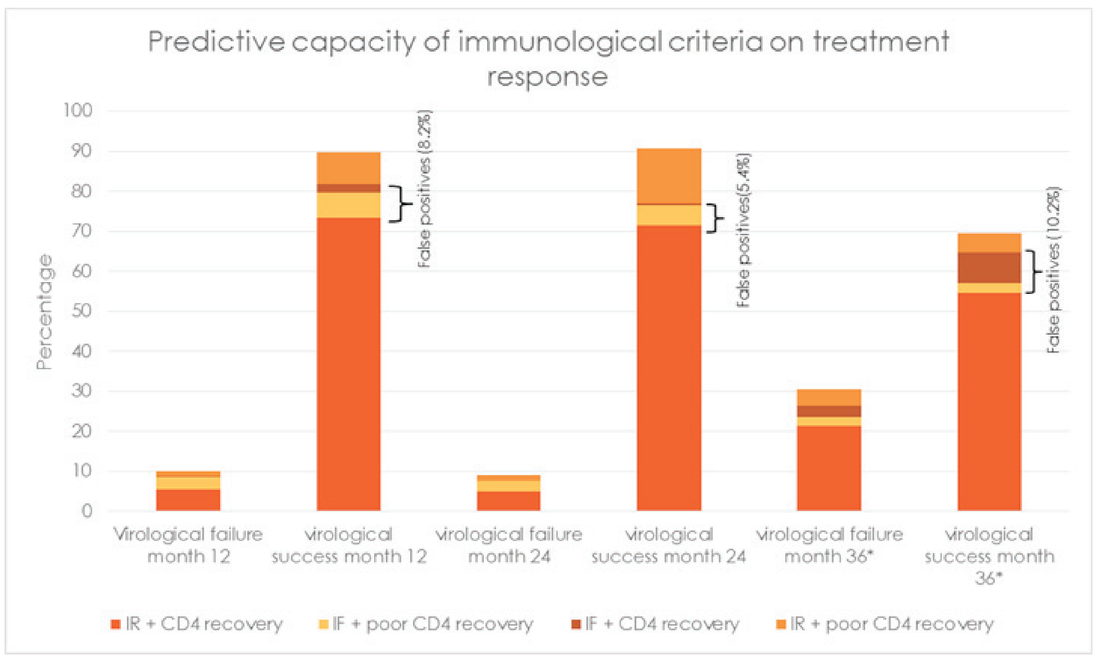
Note *In the univariate analysis the following variables were not associated with poor immunological recovery: country; public vs non-public sites; other medical conditions; HIV subtype; haemoglobin at ART initiation; viral load at baseline; year of initiation; pulmonary tuberculosis; baseline drug resistance. Only results with p-value <0.10 were included in the multivariate analysis. #statistical significant result (p<0.05).* [a] *plus Lamivudine or Emtricitabine.*

Figure 1 Kaplan-Meier HIV-related morality



Kaplan-Meier estimates of HIV-related mortality in virologically suppressed. patients after month 12 on ART.
ART = *antiretroviral therapy*

Figure 2 Impact of the poor CD4 recovery on the predictive capacity of immunological criteria on treatment response



Note *IR, Immunological response according to WHO; IF, immunological failure according to WHO; CD4 recovery (defined as a CD4 cell gain >100cells/µL or CD4 count >200 cells/µL at month 12, and a CD4 cell gain >100 cells/µL or CD4 count >350 cells/µL at month 24 and 36); virological success (defined as viral load <1000 per mL copies). * Month 36 only represents data from Zimbabwe, Nigeria and Uganda.*

affiliations

PASER PAN-AFRICAN STUDIES TO EVALUATE RESISTANCE

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