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Rate of change in CD4 counts in patients with stable HIV viremia

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BACKGROUND

- Patients may be maintained on a stable cART regimen despite having detectable levels of viremia
- PLATO (a study of patients with triple class failure) led to WHO recommendation that ARVs should be switched when viral load › 10,000 copies/ml
- Up to 90% of patients in developed countries treated with cART achieve virologic suppression while the majority of patients treated with cART live in resource limited settings and patients may be left on a virologically failing regimen (usually NNRTI)

AIMS

- Describe changes in CD4 counts in patients with stable viremia, including both patients on a stable cART regimen and those currently off antiretrovirals.
- Describe the level of viremia at which CD4 counts significantly decrease in patients on cART

METHODS

Annual CD4 slopes were calculated from 3 consecutive CD4 measurements whilst the viral load was stable, defined as ≤0.5 $\log_{10}$copies/ml difference between the highest and lowest viral loads measured at the same 3 time-points. Generalised linear models, with adjustment for repeated measurements within patients, were used to model CD4 slopes.

RESULTS

7,231 patients were included in analyses contributing 58,929 CD4 slopes. Patient characteristics are shown in **Table 1**. The unadjusted CD4 slopes are shown in **Figure 1**. Amongst those on a stable cART regimen, the CD4 count was

- Increasing by on average 40/mm³ per year when viral load ‹ 500 copies/ml
- Neither increasing or decreasing when viral loads between 500-10,000 copies/ml
- Significantly decreasing, at around 25/mm³, when viral load › 10,000 copies/ml

Among those not on antiretrovirals

- In ARV naïve, those with lower viral loads had less rapid decline in CD4 cells, but at both levels of viral load the rate of CD4 loss was greater than patients who are on cART
- The rate of loss of CD4 cells was highest in patients on treatment interruption, even though the patients have stable viremia

CD4 slopes in patients on a stable cART regimen with stable viremia

Table 2 shows the relationship between current CD4, current viral load and cART treatment regimen and CD4 slopes. After adjustment,

- In patients with a current CD4 count ≤350/mm³, the CD4 was increasing by 50/mm³ compared to 23/mm³ per year when the current CD4 count was › 500/mm³
- Adjusted CD4 increases in those on a single or boosted PI were around 40-45/mm³ per year, compared to around 30/mm³ per year for those taking an NNRTI or abacavir containing cART regimen

Comparison of cART regimens at a given level of viraemia

A priori we decided to compare CD4 count changes across regimens at specific levels of viremia for patients on a stable cART regimen. In general

- patients whose cART regimen included a boosted-PI component had the greatest increases in CD4 count whilst current viral load ‹ 500 copies/ml and the slowest decline in CD4 count when the current viral load ≥ 10,000 copies/ml
- patients taking an NNRTI-based cART regimen had a CD4 count which was decreasing when the current viral load was between 500-9,999

There was no evidence of an interaction between cART regimen and viral load (p=0.40) and this analysis had limited power.

CONCLUSIONS

- CD4 slope in patients on cART with stable viremia was significantly better than CD4 slope off cART, at all levels of viremia
- Patients taking a PI or boosted-PI regimen had significantly better CD4 slopes whilst on cART compared to patients taking NNRTIs, although patients were not randomised to treatment so confounding by indication cannot be ruled out
- The CD4 count in patients with a viral load ≥10000 copies/ml was significantly decreasing, regardless of the cART regimen being used.
- Our results support the use of a boosted-PI as a second-line regimen In resource limited settings
- These results do not provide any insight on the length of time between virologic failure and CD4 counts starting to decline. To answer this question requires information on CD4 counts and viral loads in patients maintained on a failing regimen, this may be better studied in resource limited settings as viral load testing is more routinely performed in developed countries and patients may be switched from a failing regimen more quickly
- When considering other drug classes for introduction in resource limited settings, antiviral activity, genetic barrier, and the ability to increase CD4 counts when patients are viremic should all be important considerations
- Further data is urgently required to investigate if the level of viremia at which antiretroviral treatment is switched in order to maximise CD4 counts should vary according to whether the regimen is PI or NNRTI-based

Table 1

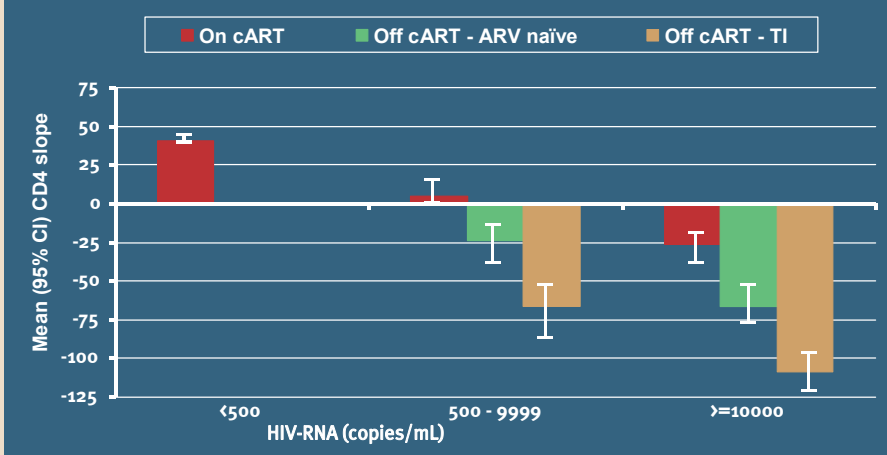
Patients (N=7231)

		N	%
Gender	Male	5549	76.7
Race	White	6168	85.3
Risk	Homosexual	3263	45.1
	IDU	1431	19.8
	Heterosexual	2019	27.9
AIDS	Yes	2038	28.2
Viral load	Median, IQR	2.00	1.70 – 3.07
Maximum VL[1]	Median, IQR	4.64	3.76 – 5.24
CD4	Median, IQR	354	220 – 529
Minimum CD4[1]	Median, IQR	168	69 – 282
Age	Median, IQR	39.3	34.3 – 46.2
Baseline	Median, IQR	5/00	9/98 – 5/03

[1]Of all laboratory values prior to baseline

Figure 1

Annual CD4 slopes in patients with stable HIV-RNA



CD4 slopes (N)	49183	3154	792	827	1612	1349	2012
Mean viral load ($\log^{10}$copies/ml)	1.68	3.31	3.22	3.28	4.57	4.62	4.72

Table 2

Adjusted annual CD4 slopes whilst on cART with a stable viral load

		Multivariate			Adjusted annual CD4 slope		
		Estimate	95% CI	P	N slopes	Mean	95% CI
Current CD4[1]	≤350	0	-	-	17617	50.3	46.8 to 53.8
	351-500	-8.6	-14.2 to -3.1	0.0023	13237	41.7	37.5 to 45.8
	›500	-27.3	-32.9 to -21.6	‹0.0001	23078	23.0	19.2 to 26.9
Current Viral load[1]	‹500	0	-	-	49170	45.3	40.1 to 50.6
	500-9999	-48.4	-57.5 to -38.8	‹0.0001	3151	-2.8	-12.2 to 6.6
	≥10000	-87.6	-98.6 to -76.5	‹0.0001	1611	-42.2	-52.2 to -32.3
cART regimen	Single PI	0	-	-	14255	43.3	38.6 to 48.0
	Boosted PI	3.6	-2.7 to 9.9	0.26	14629	46.9	42.4 to 51.5
	NNRTI	-12.2	-17.8 to -6.7	‹0.0001	21369	31.1	27.7 to 34.5
	Triple nuc	-13.1	-21.6 to -4.5	0.0028	4279	30.2	22.4 to 38.1

Multivariate model also adjusted for HIV exposure group, date of baseline, age, nucleoside pair included in regimen, time since starting antiretrovirals, development of extensive triple class failure, minimum CD4 and maximum viral load prior to baseline

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