

Abstract category: B29 Intermittent or pulsed therapy, CD4 guided therapy
Optional category: B21 Clinical trials - phase III/post-licensing

Abstract title: Progression of HIV-related disease or death (POD) in the randomised SMART study: why was the risk of POD greater in the CD4-guided ((re)-initiate ART at CD4 < 250 cells/ μ L) drug conservation (DC) vs the virological suppression (VS) arm ?

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Abstract text:

Background: SMART(n=5472) demonstrated a 2.5-fold greater risk of POD in the DC- vs VS-arm. Factors associated with this finding are reported here.

Methods: POD event (n=164) rates were calculated based on the proximal CD4 cell and HIV-RNA (VL) levels. Cox models assessed whether these levels affected the difference between arms in risk of POD and determined independent risk factors for POD in each arm.

Results: The median (IQR) of the proximal CD4 cell count prior to diagnosis of PODs was 333 cells/ μ L (246-488) and 512 (328-651) in the DC- and VS-arms, respectively. The rate of POD was higher for lower strata of proximal CD4 counts and for higher strata of VL levels in both arms, but higher in DC- vs VS-arm for CD4>350 and VL<3.5.

Table: Rates (/100 PY) according to proximal CD4 and HIV-RNA levels (% of total follow-up time in arm)

Study arm	Proximal CD4 count (cells/ μ L)				Proximal HIV-RNA (\log_{10} copies/mL)			
	<250	250-349	350-499	>499	<2.3	2.3-3.5	3.5-4.5	>4.5
DC	12.4 (8%)	4.1 (23%)	2.6 (34%)	2.5 (35%)	4.3 (21%)	2.6 (16%)	2.6 (35%)	5.2 (28%)
VS	13.7 (2%)	3.9 (6%)	1.1 (22%)	1.1 (70%)	0.8 (68%)	1.8 (17%)	3.0 (10%)	5.7 (5%)

Per design, in the DC-arm, more time was spent with lower CD4 and higher VL levels. Risk of POD in the DC-arm was associated with lower proximal CD4 counts and older age; higher proximal VL levels and older age predicted risk in VS-arm. The hazard ratio (DC/VS) for POD was reduced from 2.5 ($p<0.001$) to 1.4 ($p=0.12$) after adjustment for proximal CD4 and VL levels. Patients in DC-arm (re)-initiated ART at protocol-specified CD4 levels (232 cells/ μ L (192-299)), and achieved good CD4/VL responses (e.g. median time to VL <400copies/mL=3months; 142 CD4-cell/ μ L increase after 8 months); POD rates were similar for three 4-month intervals following ART initiation: 5.1, 5.3, and 5.7/100 PY.

Conclusions: Intended differences in proximal CD4 and VL levels between the arms of the study explains a substantial part of the difference in the risk of POD between the DC and VS arms. Additional analyses on predictors of POD will be presented.