Whilst important to consider that other Tcells such as T regs, exhausted T cells and $CD4^-$ exist within the $CD3^+/CD8^-$ population, given that the number of these cells were not of significance to alter the patterns found in our data or change the conclusions drawn they remained labelled as $CD4^+$.

Double expression of $CD38^+HLA\text{-}DR^+$ on $CD4^+$ cells was examined. Associated with increased T cell activity during active HIV infection [3] and predictors of disease progression in untreated patients [4], significantly elevated percentages of $CD38^+HLA\text{-}DR^+$ were expressed in $CD4^+$ cells in those individuals with high-level rebound/non-responses. $HLA\text{-}DR^+$ expression is indicative of T cell activation [13] whilst CD38 has numerous cellular functions involved with cell metabolism[14] and activity, and is expressed in up to 30% of $CD4^+$ cells in healthy adults [13]. Elevated in HIV, $CD4^+CD38^+$ declines when patients demonstrate successful viral control following combination ART [15].

Co-expression of $CD8^+CD38^+HLA\text{-}DR^+$ is reported to be indicative of both activation and proliferation of $CD8^+$ T-cells, reflecting strong antiviral function by exhibiting higher effector functions including proliferation, cytotoxicity and cytokine production [16, 17] however their expression is not co-dependent [18]. During hyperacute HIV infection, up to 77% of peripheral CD8+ cells express both $CD38^+$ and $HLA\text{-}DR^+$ [19], contributing towards the setpoint for an individual. However, during chronic viral infections maintaining these levels of $CD38^+HLA\text{-}DR^+$ leads to increased expression of molecules related to exhaustion and apoptosis and both elevated percentages and absolute number of $CD38^+HLA\text{-}DR^+$ predict the progression to AIDS [20].

In individuals with high-level rebound/non-response unlike the other groups, $CD8^+CD38^+HLA\text{-}DR^+$ continued to be strongly associated with viral load over 144 weeks and when normalised to circulating $CD8^+$ cells, $CD8^+CD38^+HLA\text{-}DR^+$ increased in number over time, which might suggest that as viral load comes under control, $HLA\text{-}DR^+/CD38^+$ is no longer co-expressed [21]. The strong correlation of $CD8^+CD38^+HLA\text{-}DR^+$ with viral load in participants with high-level non-response/rebound by 144 weeks from initiation of second-line therapy has been associated with a poorer outcome [22] although which is the driving factor is unclear.

In those with high-level rebound/non-response more than half of $CD8^+$ cells remained CD38 positive at week 144 although the percentages of $CD8^+$ cells expressing $CD38^+$ consistently decreased over the duration of the trial independent of viral load control.

$CD38^+$ and $HLA\text{-}DR^+$ expression are considered markers of activation that, either exclusively or co-expressed, correlate with viral load in non-controllers [23], although qualitative differences between HIV-1 specific $CD8^+$ T cell responses, such as cytokine release, can define responses of controllers and those with progressive disease [24]. Elevated $CD8^+CD38^+$ and $CD8^+HLA\text{-}DR^+$ expression persists throughout HIV infection and has prognostic significance for progression onto AIDS [23, 25].

Over the duration of the trial, whilst the percentages of $CD4^+CD38^+$ and $CD4^+$ $CD38^+HLADR^+$ T-cells decreased in all groups except high-level rebound, numbers of circulating $CD4^+CD38^+$ increased in all VL response groups when normalised to an increasing population of circulating $CD4^+$ T-cells. Thus, although the percentage of activated cells decreased with functioning ART, this was offset by an overall increase in T cell number leading to a larger pool of active cells. Therefore in absolute terms, it could be argued that ART does not lead to reduced activation. Interestingly, and potentially important, $CD8^+$ cells responded more quickly to fluctuations in viral replication [15], and generally demonstrated larger differences than $CD4^+$ parameters when comparing the high-level rebound/non-response group and other groups. This may be an important factor for long term survival of this population.

In summary, this study demonstrates that the main drivers of immune reconstitution and activation are most likely viral, rather than being driven by specific ART combinations. Immune reconstitution is impaired in high level rebound and non-responsive individuals with viral loads above 5000 copies/ml, which is well above the WHO guidelines recommend level for switching. In contrast, provided patients remain on ART, transient blips and low-level rebound have at most small effects on reconstitution and activation. These findings suggest that the current WHO viral load threshold for switching to second-line of 1000 copies/ml should avoid the most deleterious effects of high-level rebound, given that it is mostly identified through annual viral load monitoring in many low and middle income settings.

**Limitations**

In labelling our cells we have classified those $CD3^+$ $CD8^-$ as $CD4^+$ cells and acknowledge that this population of $CD8^-$ may be $CD4^-/CD8^-$. We maintain that as a percentage of cells analysed over time, our labelled $CD8^-$ follow the same independently analysed patterns of total $CD4^+$ count reported previously [2] and have therefore maintained the labelling of $CD8^-$ as $CD4^+$. In the analysis of the subsets, the significantly elevated percentages of $CD38^+$ $HLADR^+$ in $CD8^-$ cells in patients with high viral load in this study are likely to be $CD8^-CD4^+$ and not $CD8^-CD4^-$ as this population decreases with high viral load [26]**.**



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Figure 1. Number and proportion of activated CD4 and CD8 cells over time on second-line ART. Note: Showing mean plus 95% confidence interval for each randomised group at each timepoint.

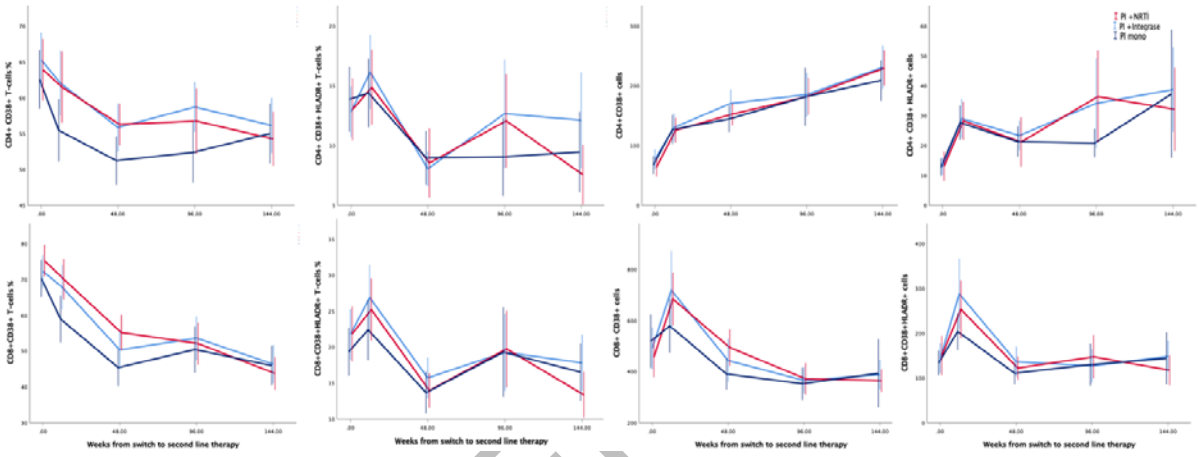


Figure 2. Viral load responses over time on second line therapy

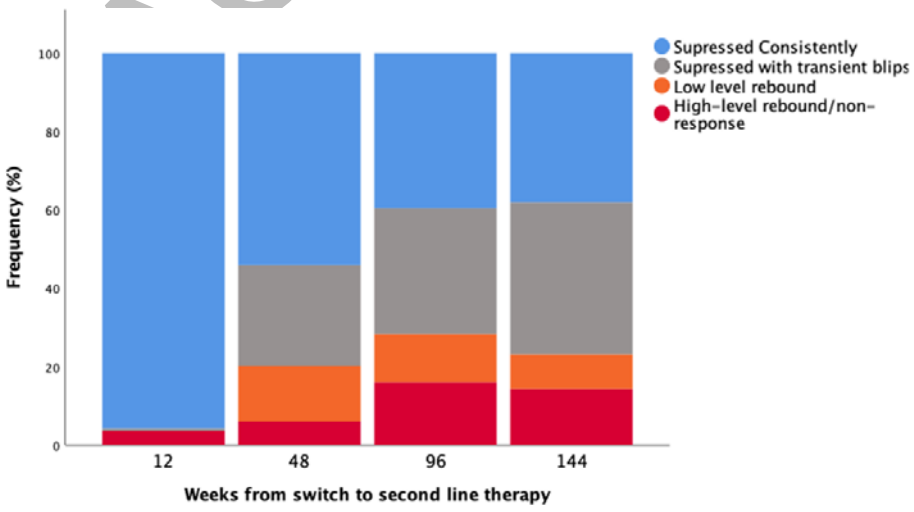

Figure 3**:** Changes in CD4 and activated CD4 sub-populations over time, expressed both as percentages and normalised to circulating CD4 levels. Note: showing mean plus 95% confidence interval for each group at each timepoint.

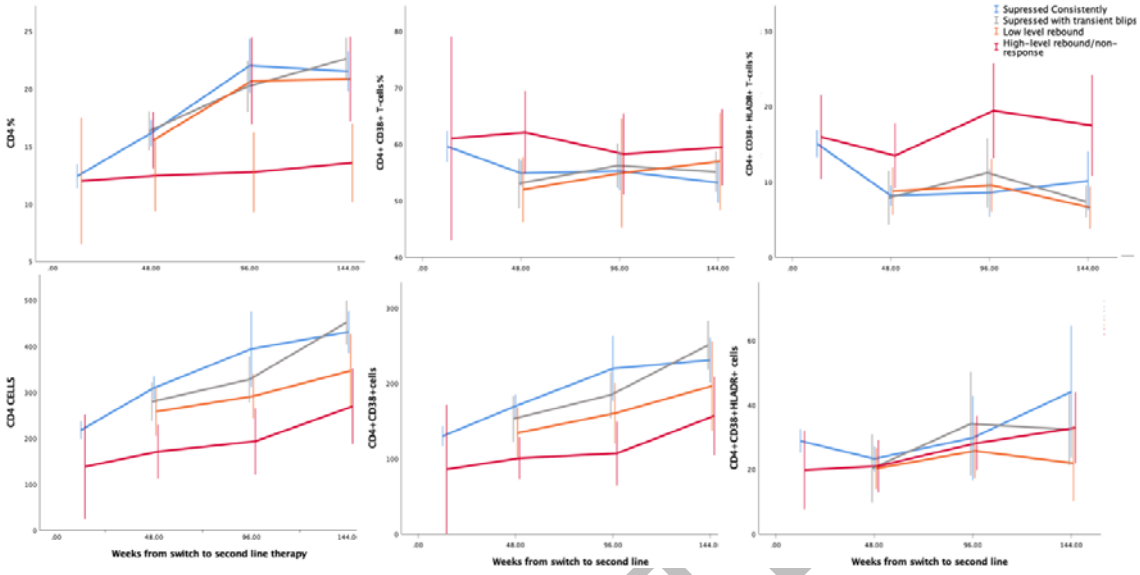


Figure 4: CD4/CD38/HLADR expression and viral load, by VL response at baseline (A), 12 weeks (B), 48 weeks (C), 96 weeks (D) and 144 weeks (E) for viral loads >40 copies/ml. Note: Definition of suppressed consistently at 12 weeks includes VL response

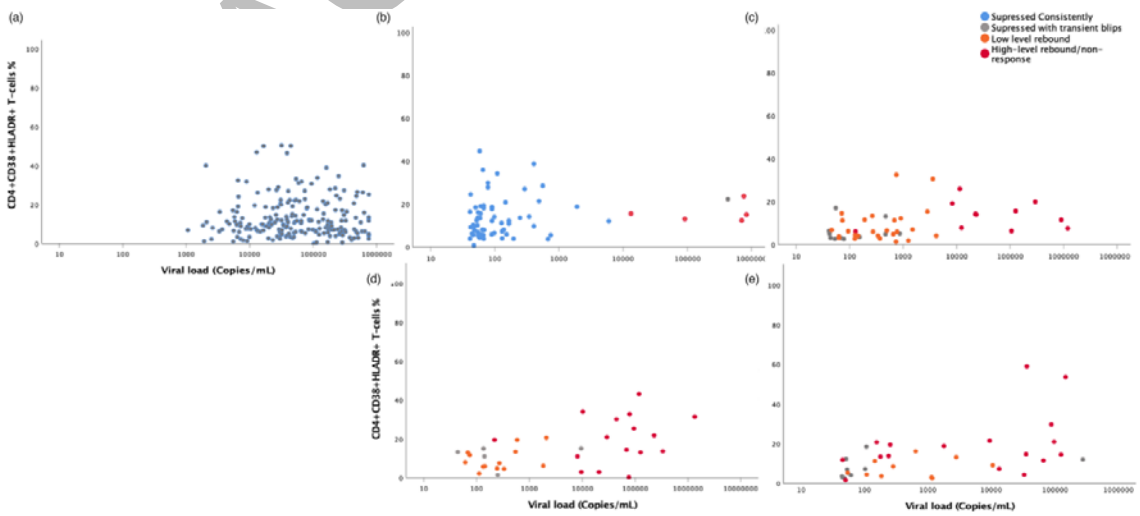

Figure 5: Changes in CD8 and activated CD8 sub-populations over time, expressed both as percentages and normalised to circulating CD8 levels. Note: Showing mean plus 95% confidence interval for each group at each timepoint.

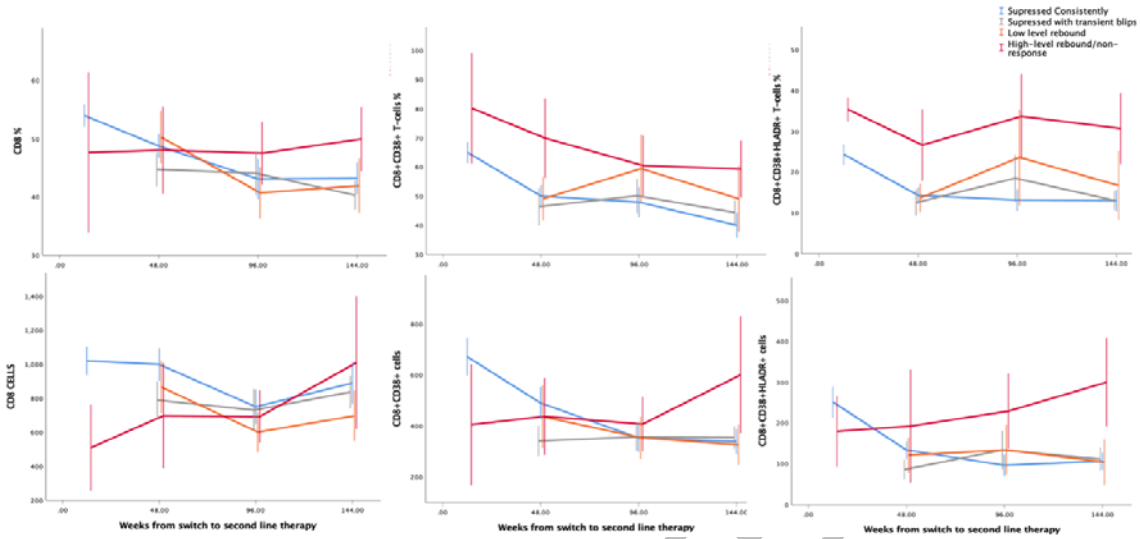

**Table 1: Cell numbers and subpopulations over 144 weeks on second-line therapy.**

| | Weeks from switch to second-line therapy | | | p | Weeks from switch to second-line therapy | | p | p | p |
|---|---|---|---|---|---|---|---|---|---|
| Weeks on Second Line Therapy | **0** | **12** | **48** | **Week 48 V 0** | **96** | **144** | **week 144 v 0** | **week 144 v 12** | **week 144 v 48** |
| Numbers with results | 208 | 140 | 183 | | 106 | 147 | | ANCOVA adjusted for BL | |
| CD4 cells/mm$^3$ | 112 (98 to 125) N=193 | 213 (194 to 232) | 286 (267 to 305) N=182 | p<0.0005 | 328 (288 to 367) | 408 (378 to 438) | p<0.0005 | p<0.0005 | p<0.0005 |
| CD4 % | 10 (9 to 11) N=193 | 12 (11 to 13) | 16 (15 to 17) N=182 | p<0.0005 | 20 (18 to 21) | 21 (20 to 22) | p<0.0005 | p<0.0005 | p<0.0005 |
| CD4+ CD38+ T-cells % | 64 (62 to 66) | 60 (57 to 62) | 55 (53 to 56) | p<0.0005 | 56 (54 to 58) | 55 (53 to 57) | p<0.0005 | p=0.001 | p=0.85 |
| CD4+CD38+HLADR+ T-cells % | 13 (12 to 15) | 15 (13 to 17) | 9 (7 to 10) | p<0.0005 | 11 (9 to 14) | 10 (8 to 12) | p=0.003 | p<0.0005 | p=0.39 |
| CD4+CD38+ cells | 69 (60 to 78) | 127 (114 to 140) | 156 (144 to 168) | p<0.0005 | 183 (161 to | 224 (205 to 243) | p<0.0005 | p<0.0005 | p<0.0005 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N=193 | | N=182 | | 205) | | | | |
| CD4+CD38+HLADR+ cells | 13 (11 to 15)<br><br>N=193 | 28 (25 to 32) | 22 (18 to 25)<br><br>N=182 | p<0.0005 | 30 (23 to 38) | 36 (27 to 45) | p<0.0005 | p=0.052 | p<0.0005 |
| | **Weeks from switch to second-line therapy** | | | **p** | **Weeks from switch to second-line therapy** | | **p** | **p** | **p** |
| CD8 Cells | 690 (627 to 753)<br><br>N=193 | 999 (917 to 1081) | 908 (842 to 974)<br><br>N=182 | p<0.0005 | 716 (655 to 777) | 867 (787 to 947) | p<0.0005 | p<0.0005 | p=0.361 |
| CD8 % | 58 (57 to 60)<br><br>N=193 | 54 (52 to 56) | 48 (46 to 49)<br><br>N=182 | p<0.0005 | 44 (42 to 46) | 43 (41 to 45)<br><br>N=146 | p<0.0005 | p<0.0005 | p<0.0005 |
| CD8+CD38+ T-cells % | 73 (70 to 76) | 66 (62 to 69) | 50 (47 to 53) | p<0.0005 | 52 (49 to 55) | 45 (42 to 48) | p<0.0005 | p<0.0005 | p=0.02 |
| CD8+CD38+HLADR+ T-cells % | 21 (19 to 23) | 25 (22 to 27) | 14 (13 to 16) | p<0.0005 | 19 (16 to 23) | 16 (14 to 18) | p<0.0005 | p<0.0005 | p=0.66 |
| CD8+CD38+ cells | 488 (438 to 537) | 661 (590 to 732) | 441 (399 to 483) | p=0.094 | 362 (330 to | 378 (336 to 420) | p<0.0005 | p<0.0005 | p=0.04 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N=193 | | N=182 | | 395) | | | | |
| CD8+CD38+HLADR+ cells | 143 (122 to 163) N=193 | 249 (212 to 285) | 123 (107 to 139) N=182 | p=0.067 | 134 (109 to 159) | 134 (112 to 157) | p=0.104 | p<0.0005 | p=0.53 |
| CD4:CD8 ratio | 0.2 (0.2 to 0.2) N=193 | 0.3 (0.2 to 0.3) | 0.4 (0.3 to 0.4) N=182 | p<0.0005 | 0.5 (0.4 to 0.5) | 0.5 (0.5 to 0.6) | p<0.0005 | p<0.0005 | p<0.0005 |

Note: showing mean and 95% confidence interval for each randomised group at each timepoint. 208 patients were immunophenoptyped at baseline; 193 patients had CD4 and CD8 data on the same sample as immunophenotyping at baseline (15 had CD4 and CD8 on screening sample only)