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 should be switched when viral load > 10,000 copies/ml

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 viroemia 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 log10 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
7,273 patients were included in analyses contributing 58,929 CD4 slopes. Patient characteristics are shown in Table 1. The adjusted CD4 slopes are shown in Figure 1. Among those on a stable cART regimen, the CD4 count was:
- Increasing by an 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 per year when viral load > 10,000 copies/ml

Among those not on antiretrovirals:
- In ARV naive, 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
- In patients with a current CD4 count ≥500/mm3, the CD4 was increasing by 50/mm3 compared to 25/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 viremia
- 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 NNRTI, although patients were not randomised to treatment so confounding by indication cannot be ruled out

- The CD4 count in patients with a viral load ≥10,000 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, which 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 viroemia 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)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5549</td>
<td>1682</td>
</tr>
<tr>
<td>%</td>
<td>77.6</td>
<td>22.4</td>
</tr>
</tbody>
</table>

Table 2: Adjusted annual CD4 slopes whilst on cART with a stable viral load

<table>
<thead>
<tr>
<th>Current</th>
<th>2500</th>
<th>2500 - 9999</th>
<th>≥10000</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4</td>
<td>0.6</td>
<td>-3.1 to -0.3</td>
<td>0.030</td>
</tr>
<tr>
<td>Current</td>
<td>2500</td>
<td>≤4.6</td>
<td>≤4.6</td>
</tr>
<tr>
<td>CD4</td>
<td>-27.3</td>
<td>-51.9 to -12.6</td>
<td>0.0002</td>
</tr>
<tr>
<td>Viral load</td>
<td>≤500</td>
<td>500 - 9999</td>
<td>≥10000</td>
</tr>
<tr>
<td>PI</td>
<td>-18.6</td>
<td>-26.4 to -9.8</td>
<td>0.0005</td>
</tr>
<tr>
<td>NNRTI</td>
<td>-8.6</td>
<td>-17.0 to -0.9</td>
<td>0.0007</td>
</tr>
<tr>
<td>NNRTI</td>
<td>-52.2</td>
<td>-17.8 to -6.7</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

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

Figure 1: Annual CD4 slopes in patients with stable HIV-RNA

Figure 2: Mean annual CD4 slopes in patients on stable cART with stable viroemia and those currently off antiretrovirals.