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Abstract #S-153
Poster #890

Immunologic and viral dynamics among HIV-infected children after planned treatment interruption: a substudy of the Paediatric European Network for Treatment of AIDS (PENTA) 11 trial.

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Background/Objectives

A multi-centre randomised open phase II trial (PENTA 11) was performed to determine whether children with chronic HIV infection undergoing planned antiretroviral (ART) treatment interruptions were disadvantaged clinically, immunologically or virologically by periods of time off ART.

HIV- infected children aged 2 to 15 years old, on any ART regimen containing 3 or more drugs which they had taken for at least 24 weeks, with a CD4% >30% (2-6 yrs) or CD4 > 25% and > 500 cells/mm3 (>7yrs) and an HIV-1 RNA <50c/ml were randomised to Continuous ART (CT: continue their current regimen) or to CD4-guided Planned Treatment Interruptions (PTI) (further details of the trial can be found in *AIDS* 2010,24:231-241).

While no serious short-term clinical events were observed, a detailed substudy evaluated the influence of PTI on immunological and viral dynamics.

Methods

109 children were randomised to CT (53) or PTI (56), and had CD4 and CD8 measured every 12 weeks. CD4 and CD8 RA/RO phenotypes were also measured routinely in some children.

In 36 (18 PTI,18 CT) children (UK and Italy) detailed immunophenotyping of CD4, CD8, CD45RA, CD31, Ki67, HLA-DR and CD38, and cell-associated DNA were performed on available samples at 0, 2, 4, 8, 12 and 12 weekly. Figure 1 shows the schema for the CD4 cell populations investigated. The combination of antibodies used allows for the identification of recent thymic emigrants (RTE), central naïve and memory cells. The levels of proliferation and activation were assessed within each of these populations by staining for Ki67 and HLA-DR. CD8 cell populations were also investigated using CD45RA and activation determined by CD38 expression. Proviral DNA was using a QPCR assay.

Changes from baseline were estimated using normal regression of actual measurements adjusting for baseline

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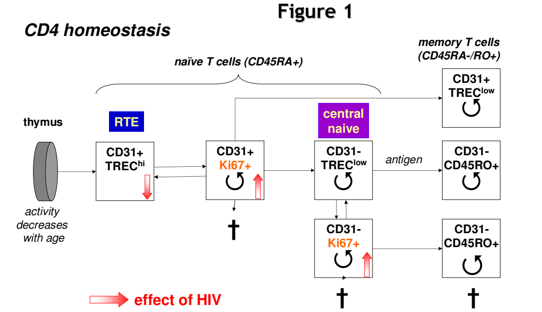
Figure 1



Results

At baseline the median age was 9 (range 2-16) years, median CD4% was 37% (IQR: 33,41) and CD4 990 (763,1248) cells/mm^3.

In the PTI arm, CD4 cell count fell rapidly in the first 12 weeks off ART, while the CD8 cell count rose significantly in the same period (Figure 2).

This was predominantly due to a early reduction in CD45RA+CD31+ in the first 4 weeks (mean (SE) change 0-4 weeks -230 (38) cells/mm^3) (Figure 3), and slower decline in CD45RA-CD31- cells (mean (SE) change 0-12 weeks -126(17) cells/mm^3).

The increase in CD8 cells over this time was due to an increase in CD45RO cells (mean (SE) change 0-12 weeks +244(71) cells/mm^3).

However by 12 weeks, relative proportions of CD4 sub-populations had returned to near baseline levels, albeit at a lower but relatively stable CD4 (Figure 4), while the CD8 sub-populations remained stable from 12 weeks but markedly different from baseline and from the CT arm (Figure 5).

The loss of CD4 in the PTI arm was associated with increased expression of Ki67 and HLA-DR, particularly in the CD45RA-CD31- population (Ki67: Mean (SE) change 0-4 weeks in % expression was -0.4 (0.5) CT vs 2.7 (0.5) PTI, p=0.004, Figure 6). HLA-DR: -2.3 (1.1) CT vs 1.0 (0.8) PTI ,p=0.04). Similar increases were seen in CD38 expression in CD8 cells.

There was also some evidence that the proportions of cells containing HIV DNA increased in the PTI arm (mean (SE) change 0-4 weeks 0 (0.2) CT vs 0.5 (0.1) PTI $\log^{10}$ copies/10^6 peripheral blood mononuclear cells (PBMC), p=0.04) (Figure 7).

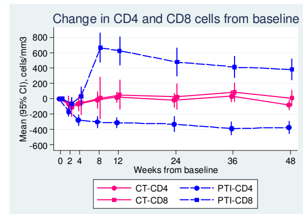


Figure 2

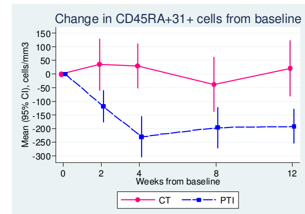


Figure 3

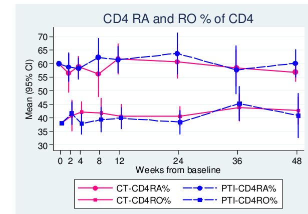


Figure 4

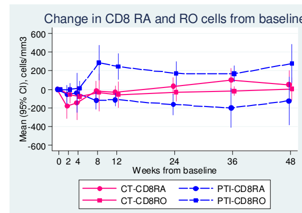


Figure 5

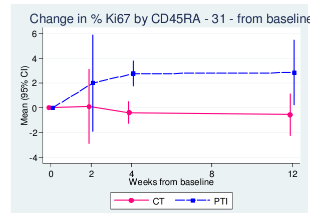


Figure 6

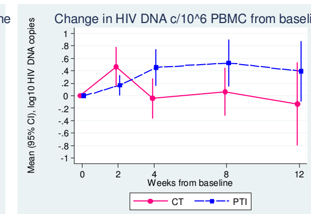


Figure 7

Conclusions

After PTI in children with well controlled viraemia, a substantial CD4 reduction, through loss of both RTE and memory cells, was observed in the first 12 weeks off ART. This coincided with increased viral load and immune activation. However, after 12 weeks the relative proportions of CD4 cell sub-populations rapidly returned towards baseline levels and those seen in the CT arm. In contrast the CD8 count rose rapidly due to an increase in CD45RO cells in the first 12 weeks. However the relative proportions of RA and RO cells remained stable until 48 weeks.

The mechanisms maintaining these populations are not fully understood but the increase in HLA-DR and Ki67 throughout PTI suggests that maintaining this balance comes at the expense of increased cell activation, proliferation and probably cell death.

A 5-year follow-up of children in PENTA 11 is ongoing and necessary to evaluate the long-term, clinical, immunological and virological implications of PTI.