

## Background

Guidelines recommend as first therapy either the NNRTI efavirenz (EFV) or a PI such as lopinavir boosted with low dose ritonavir (LPV/r). Previous observational studies comparing these two first therapies gave different results to those seen in the only large randomised trial to date (ACTG 5142). Using data from the Swiss HIV Cohort Study, we investigate the relative benefits of EFV and LPV/r as first therapy, particularly for patients with advanced infection.

## Methods

We analyse data from all treatment naive patients starting either EFV or LPV/r and the two NRTIs lamivudine and zidovudine. We fit proportional hazards models to these data; then add an interaction term to each model to show how the relative effect of therapy is modified by the CD4 cell count when starting therapy.

## Results

Our sample consists of 1201 patients: 660 starting EFV with a median follow up of 4.5 years and 541 starting LPV/r with a median follow up of 3.1 years.

Under both therapies 35% of patients experienced virologic failure according to the definition in the 2008 DHHS guidelines, but on average patients starting EFV have been followed for longer (Figure 1). The adjusted hazard ratio (HR, 95% CI) for virologic failure shows an advantage for EFV therapy over LPV/r (0.63, 0.50-0.78). Adding an interaction term shows that for each 100/mm<sup>3</sup> lower CD4 cell count when starting therapy, this HR for therapy is then multiplied by a factor of 1.00 (0.90-1.12).

We define an expected rate of immune recovery as the annual CD4 increase achieved by at least 80% of patients with viral suppression according to EuroSIDA statistics that are cross-classified by CD4 cell count when starting therapy and number of years on therapy. This expected rate of CD4 cell increase was not achieved by 19% and 23% of patients starting EFV and LPV/r respectively. The adjusted HR shows an advantage for EFV therapy over LPV/r (0.68, 0.51-0.91). However adding an interaction term shows that for each 100/mm<sup>3</sup> lower CD4 cell count when starting therapy, this HR for therapy is then multiplied by a factor of 1.29 (1.14-1.46). This result is consistent with changes seen in the CD4 cell count over time (Figure 2).

## Conclusions

Patients on EFV appear to have a lower risk of virologic failure than patients on LPV/r and this risk seems independent of their CD4 count when starting therapy. Patients on EFV also appear more likely to maintain an expected rate of CD4 cell increase but this advantage disappears if they start therapy with a low CD4 cell count.

## How do these results differ from ACTG 5142?

In the trial, there was no difference in the risk of virologic failure between the two therapies in patients with a baseline CD4 cell count below 100 cells/mm<sup>3</sup>. However the trial was not powered to detect subgroup differences. Our results suggest that virologic failure is less likely with EFV regardless of baseline CD4 cell count.

In the trial, greater increases in CD4 cell count were seen in patients on LPV/r. Our results suggest patients starting EFV are more likely to achieve expected CD4 cell increases unless patients start with a low CD4 cell count. Patients in our study started therapy with higher CD4 cell counts (median 270 and 220 cells/mm<sup>3</sup> for EFV and LPV/r) than those in the trial (median 190 cells/mm<sup>3</sup>). The longer follow up in our study (median 4.5 and 3.1 years for EFV and LPV/r) than in the trial (median 2.2 years) may also contribute to apparently contradictory results. If EFV is less likely to lead to virologic failure, in time this must represent an advantage for immune recovery as well.

Figure 1: Kaplan Meier curve for virologic failure

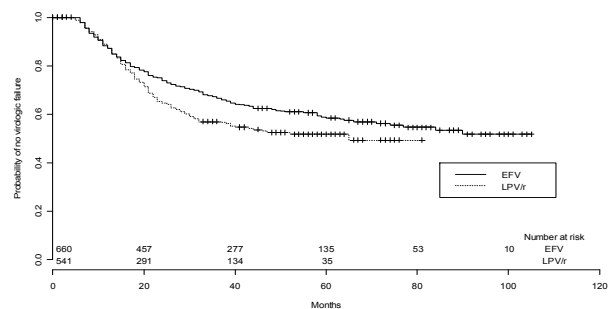


Figure 2: CD4 cell count response curves for patients starting therapy with a count ≤ 200 cells/mm<sup>3</sup> (left) or > 200 cells/mm<sup>3</sup> (right)

