BACKGROUND
Etravirine (ETR) is a potent new NNRTI that retains antiviral activity against NNRTI-resistant viruses. This activity, however, declines as NNRTI-associated resistance mutations accumulate. An understanding of the rate of NNRTI resistance accumulation under the pressure of nevirapine or efavirenz in the presence of detectable viral load is essential to predict the activity and potential benefit of subsequent use of ETR in this clinical setting. The results of this analysis may also have implications for therapy planning in the resource-limited setting (6,8).

OBJECTIVES
To describe the population of patients in EuroSIDA who remained on a failing NNRTI-based regimen some time after experiencing virological failure in an NNRTI and to identify patients with genotypic tests that were available while drug was present. Treatment with ETR was omitted.

STUDY DESIGN - METHODS
Patients enrolled in EuroSIDA with ≥2 available genotypic resistance tests (GRT) provided the first GRT after the date of virological failure of nevirapine (NNRTI: efavirenz) and that the same NNRTI was kept at the time of the 2nd GRT (i.e. nevirapine or efavirenz). Plasma viral load (VL) had to be detected at the time of the 2nd GRT.

RESULTS
A total of 87 patients with a genotype were included. The median VL at the time of the first GRT was 5.0 log10 copies/mL (IQR 4.2-5.8). The corresponding figures for 118 patients with two or more GRTs with a median number of 2 VL values over this time period were observed at a very stable VL with a median VL of 5.0 log10 copies/mL (IQR 4.2-5.8). The corresponding figures for 118 patients with two or more GRTs with a median number of 2 VL values over this time period were observed at a very stable VL with a median VL of 5.0 log10 copies/mL (IQR 4.2-5.8).

CONCLUSIONS
It is possible that our patients are a selected sample of patients whose therapy has not been switched because viral load did not dramatically change between GRTs. The impact of resistance accumulation over a long period on the response to ETR-containing regimens remains to be seen.

LIMITATIONS
The main limitation of this analysis is the small sample size of patients.

Table 1: Main characteristics at time of first GRT (t0) were described and average changes in laboratory markers from t0 (time of 2nd GRT) were evaluated. The Rega interpretation system (IS version 7.1) was used to predict the number of active drug in the ART regimen at t0. In this analysis, it was assumed that NNRTI-associated mutations identified at t0 was still present at t1. The rate of NNRTI resistance accumulation was calculated as number of new mutations per person-years of follow-up (PYFU). Analyses were repeated in patients in which EFV were not included in the failing regimen and in those with 3 or 5 NNRTI mutations detected at first GRT. A multidisciplinary database of patients was performed to identify independent predictors of TAM accumulation. The model properly accounted for the fact that a patient who contributed more than one pair of genotypes and that this patient could not be assumed to be independent observations. Rega-predicted susceptibility to NNRTI was calculated at t0 and t1, the change calculated for each patient and the mean predicted reduction in susceptibility was estimated.

Table 2: Table shows the greater was the susceptibility to the NNRTI used in the failing regimen, the faster was the rate of accumulation of resistance comparing pairs failing on NVP with those failing on EFV. The only two factors associated with the rate of accumulation of ETR mutations were the predicted susceptibility to the NNRTI used (again, the rate of accumulation was a fold factor if viruses were predicted to be intermediate or sensitive compared to resistant) and gender (the rate of accumulation tended to be slower by 86% in females compared to males, p=0.05).

Table 3: Predictors of accumulation of NNRTI-associated resistance.

Table 4: Predictors of accumulation of NNRTI-associated resistance.

Table 5: Table shows that the greater was the susceptibility to the NNRTI used in the failing regimen, the faster was the rate of accumulation of resistance.

Antiretrovirals
For the pairs of HIV patients on a NVP and EFV-containing regimen (Table 3). At first GRT is a pair, the median number of drugs in both groups was a 2 (range 0-4) and the most frequently used nucleosides at t0 with NNRTI were lamivudine (64%), stavudine (47%) and didanosine (41%). In 193 (62%) of the failing regimens at a protease inhibitors were used. The frequency of use of antiretroviral includes NNRTI at t0 is similar to that observed at t1, suggesting that these patients had been kept on exactly the same drugs over its virological fall.

HIV drug resistance
Table 3 shows the distribution of NNRTI mutations and groups of RT mutations detected in major virus populations at t0 and the estimated proportions at t1 (under the assumption of indefinite persistence of mutations once detected).

Rate of accumulation of resistance
The number of pairs for which there was at least one NNRTI mutation that was detected at t0 but not at t1 was 64 (97%). Overall, 24 (16%) NNRTI resistance mutations were accumulated over 500 PYFU (45% per year, 95% CI: 30-60), and the rate was 0.36 (0.3-0.4) mutations per 500 PYFU in those with a virus predicted to be resistant, 0.55 per year (95% CI: 0.29-0.74, 7 mutations over 2.6 PYFU) in those predicted to have intermediate resistance and 2.71/year (95% CI: 1.15-4.93, 7 mutations over 2.6 PYFU) in those predicted to be susceptible to the NNRTI used.

The estimated rate of accumulation of NNRTI-specific mutations was slower than the overall NNRTI accumulation. As new NNRTI-specific mutations were detected, the estimated rate of accumulation of NNRTI-specific mutations was reduced from a mean of 59% to a mean of 55% (absolute mean change of 4% over t0-t1 or 8%/year, Table 4).

Table 6: Table shows that the greater was the susceptibility to the NNRTI used in the failing regimen, the faster was the rate of accumulation of resistance. After restricting the analysis to pairs in which NVP was the NNRTI used at the time of the first GRT in the pair there was a 0.58 (0.57-0.59) reduction in the rate of accumulation of resistance comparing pairs failing on NVP with those failing on EFV. The only two factors associated with the rate of accumulation of ETR mutations were the predicted susceptibility to the NNRTI used (again, the rate of accumulation was a fold factor if viruses were predicted to be intermediate or sensitive compared to resistant) and gender (the rate of accumulation tended to be slower by 86% in females compared to males, p=0.05).

Table 7: Table shows that the greater was the susceptibility to the NNRTI used in the failing regimen, the faster was the rate of accumulation of resistance.