

# Comparison of Etravirine Resistance and Efavirenz/Nevirapine Resistance among HIV-1 Infected Patients Who Experienced Virologic Failure with NNRTI-based Antiretroviral Therapy

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## ABSTRACT

**Background:** Resistance-associated mutations (RAMs) of etravirine (ETV) and efavirenz/nevirapine (EFV/NVP) are not the same. ETV has activity against EFV/NVP-resistant HIV-1 if ETV RAMs are <3. This study aimed to compare ETV and EFV/NVP resistance among HIV-1 infected patients who had virologic failure with NNRTI-based antiretroviral therapy (ART).

**Methods:** Genotype resistance assay was conducted in a cohort of HIV-1 infected patients who experienced virological failure from NNRTI-based regimen. We focused on ETV RAMs and EFV/NVP RAMs described by IAS-USA 2008.

**Results:** A total of 134 patients (mean ± SD age, 41.7 ± 8.5 years; 60% male) were studied. Eighty-three (62%) patients received NVP; the others received EFV. At failure, the median (IQR) duration of ART was 32 (17-52) months. The mean ± SD CD4 cell count and median (IQR) HIV-1 RNA were 221 ± 158 cells/mm<sup>3</sup> and 4.1 (3.7 - 4.6) log copies/mL, respectively. Of 134 patients, 90 (69%) had EFV/NVP resistance (≥1 EFV/NVP RAMs) and 8 (6%) had ETV resistance (≥3 ETV RAMs). Among patients with EFV/NVP resistance, 9% had ETV resistance. There were no differences of demographics, EFV or NVP use, duration of ART, CD4 cell counts, HIV-1 RNA between patients who had and did not have ETV resistance (p >0.05). No clinical factor was found to be associated with ETV resistance in logistic regression. All patients with ETV resistance had EFV/NVP resistance. Patients with ETV resistance had a higher rate of K65R (25% vs. 6%, p = 0.033) when compared to patients without ETV resistance.

**Conclusions:** Most patients who experienced virologic failure with NNRTI-based ART have EFV/NVP resistance whereas a small proportion of patients have ETV resistance. There is no clinical factor to predict ETV resistance and HIV-1 genotype testing is needed to identify this group.

## BACKGROUND

Treatment options after failing an initial regimen of antiretroviral therapy (ART) in resource-limited settings are markedly limited. Etravirine (ETV) has demonstrated activity against NNRTI-resistant HIV-1 in DUET-1 and DUET-2 study but its efficacy depends on the number of etravirine resistance-associated mutations (RAMs). Resistance-associated mutations (RAMs) of etravirine (ETV) and efavirenz/nevirapine (EFV/NVP) are not the same. ETV has activity against EFV/NVP-resistant HIV-1 if the number of ETV RAMs, described by IAS-USA 2008, are less than 3. This study aimed to compare ETV and EFV/NVP resistance among HIV-1 infected patients who had virologic failure with an initial regimen of NNRTI-based antiretroviral therapy (ART) in a resource-limited setting.

## MATERIALS AND METHODS

A cohort study was conducted among HIV-1-infected patients who were diagnosed virological failure from an initial regimen of NNRTI-based ART between January 2004 and June 2008 at Ramathibodi Hospital, Mahidol University and Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Thailand. Inclusion criteria included HIV-1-infected patients >15 years of age who had received an NNRTI-based ART as an initial regimen, achieved undetectable HIV RNA at 4-6 months after initiation of ART and subsequently had virological failure documented by two consecutive HIV RNA assays of > 1000 copies/mL. HIV-1 genotypic resistance testing was conducted.

The TRUGENE HIV-1 Genotyping Assay was used in conjunction with the Open Gene automated DNA sequencing system (Visible Genetics Inc., Toronto, Canada) to sequence the RT and PR regions of the HIV-1 cDNA. Mutations critical to the HIV-1 reverse transcriptase and protease sequences were reviewed from the results of genotypic resistance tests. We focused on ETV RAMs previously described by IAS-USA 2008: V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, and G190A/S. Proportion and predicting factors of patients with <3 etravirine-RAMs were evaluated. All analyses were performed using SPSS version 13.0. A p value less than 0.05 was considered statistically significant. The study was reviewed and approved from the institute review board.

## RESULTS

A total of 134 patients with a mean (±SD) age of 41.7 (±8.5) years were studied. Eighty (60%) patients were male. Prior to virologic failure, 83 (62%) patients received NVP-based ART; the others received EFV-based ART. At failure, the median (IQR) duration of ART was 32 (17-52) months. The mean (±SD) CD4 cell count and median (IQR) HIV-1 RNA were 221 (±158) cells/mm<sup>3</sup> and 4.1 (3.7 - 4.6) log copies/mL, respectively. Of 134 patients, 90 (69%) had EFV/NVP resistance (≥1 EFV/NVP RAMs) and 8 (6%) had ETV resistance (≥3 ETV RAMs). There were no differences of demographics, EFV or NVP use, duration of ART, CD4 cell counts, HIV-1 RNA between patients who had and did not have ETV resistance (p >0.05). From logistic regression, no clinical factor was found to be associated with ETV resistance (Table 1). Among 90 patients with EFV/NVP resistance, 8 (9%) had ETV resistance whereas all patients with ETV resistance had EFV/NVP resistance.

Table 1. Clinical characteristics of 134 patients who had virologic failure with an initial NNRTI-based ART

Characteristics	Number of etravirine RAMs		P value
	<3 (n=126)	≥3 (n=8)	
Male gender, number (%)	76 (60.3)	4 (50)	0.411
Age, mean (SD), years	41.7 (8.5)	41.1 (9.4)	0.764
Duration of ART, median (IQR), months	32.0 (17.7 - 52.6)	35.6 (13.8 - 51.1)	0.820
Prior ART regimen, number of patients (%)			
- NRTIs backbone:			0.597
d4T + 3TC	112 (88.9)	6 (75.0)	
AZT + 3TC	3 (2.4)	1 (12.5)	
AZT + ddl	11 (8.7)	1 (12.5)	
- NNRTI:			0.404
Nevirapine	77 (61.1)	6 (75.0)	
Efavirenz	49 (38.9)	2 (25.0)	
CD4 cell counts at virological failure, median (IQR), cells/mm <sup>3</sup>	185 (105 - 340)	168 (30 - 270)	0.283
HIV RNA at virological failure, median (IQR), log copies/mL	4.1 (3.7 - 4.5)	4.4 (3.8 - 5.0)	0.324

Regarding associated NRTI RAMs, patients with ETV resistance had a higher rate of K65R (25% vs. 6%, p = 0.033) when compared to patients without ETV resistance. There were no differences of other NRTI RAMs including TAMs, M184V, L74V, and Q151M.

## CONCLUSIONS

Most patients who experienced virologic failure with an initial regimen of NNRTI-based ART have EFV/NVP resistance whereas a small proportion of patients have ETV resistance. ETV is another antiretroviral agent that can be used in the second ART regimen in resource-limited settings. However, there is no clinical factor to predict ETV resistance at virologic failure from NNRTI-based regimen and HIV-1 genotype testing is needed to identify patients who can use ETV in the second ART regimen.