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Evaluating the Role of Etravirine in the Second-line ART after Failing an Initial NNRTI-based Regimen in a Resource-limited Setting

Contact: S Sungkanuparph
rasuy@mahidol.ac.th

Somnuek Sungkanuparph [1], Weerawat Manosuthi [1,2], Sasisopin Kiertiburanakul [1], Bucha Piyavong [1], Wasun Chantratita [1]

[1] Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400; [2] Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health, Nonthaburi, 11000, Thailand

ABSTRACT

Etravirine demonstrates 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). This study aimed to evaluate the role of etravirine in the second-line ART in a resource-limited setting. Genotype resistance mutation patterns in a cohort of HIV-1 infected patients who experienced virological failure from an initial NNRTI-based regimen. We focused on etravirine-RAMs previously described: 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. There were 158 patients with a median duration of ART prior to failure of 22 months. The median CD4 cell count and HIV-1 RNA at the time of virological failure were 173 cells/mm3 and 4.1 log copies/mL, respectively. Of 158 patients, 131 (82.9%) had etravirine-RAMs and 92 (58.2%) had <3 etravirine-RAMs. From logistic regression, there was no clinical factor to predict patients with <3 etravirine-RAMs. Of 92 patients with <3 etravirine-RAMs, 69 (75%) had ≥2 active NRTIs from the genotype results. In resource-limited setting, three-fourths of patients who fail an initial NNRTI-based regimen can use etravirine in the second-line ART; and genotype testing is needed to identify this group. Three-fourths of these patients, indicated by genotype results, may be able to use etravirine plus 2 active NRTIs for the second regimen. This strategy may be an option for patients who cannot afford or tolerate protease inhibitor. Prospective study to evaluate this strategy should be conducted in resource-limited setting.

BACKGROUND

Treatment options after failing an initial regimen of antiretroviral therapy (ART) in resource-limited settings are markedly limited because of the extensive cross-resistance to NRTIs secondary to late detection of failure. Etravirine (TMC125) demonstrates 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). This study aimed to evaluate the role of etravirine in the second-line ART in a resource-limited setting.

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 December 2007 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 etravirine-RAMs previously described: 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 12.0. A p value less than 0.05 was considered statistically significant. The study was reviewed and approved from the institute review board.

RESULTS

There were 158 patients with a mean (SD) age of 36.5 (7.0) years and 65.2% were males. 133 (84.2%) patients received nevirapine-based ART; the others received efavirenz-based ART. The median (IQR) duration of ART prior to failure was 22 (13-29) months. The median (IQR) of CD4 cell count and HIV-1 RNA at the time of virological failure detection were 173 (98-261) cells/mm^3 and 4.1 (3.7-4.7) log copies/mL, respectively. Of 158 patients, 131 (82.9%) had etravirine-RAMs including Y181C/I/V (59.5%), G190A/S (33.5%), V179D/F (8.4%), V106I (4.4%), V90I (0.8%), A98G (0.8%), L100I (0.8%), and K101E/P (0.8%). Of 131 patients with etravirine-RAMs, 92 (70.2%) had <3 etravirine-RAMs. This accounts for 58.2% (92/158) of all patients. Totally, 75.3% of all patients who failed an initial NNRTI-based ART can use etravirine in the second-line ART.

There were no differences of demographics, CD4 cell count, and HIV-1 RNA level at the time of failure between patients with <3 and ≥3 etravirine-RAMs (Table 1). From logistic regression, there was no clinical factor to predict patients with <3 etravirine-RAMs. Of 119 patients who had no or <3 etravirine-RAMs, 89 (74.8%) had ≥2 active NRTIs from the genotype results.

Figure 1. Etravirine-RAMs among 158 patients who failed an initial NNRTI-based ART

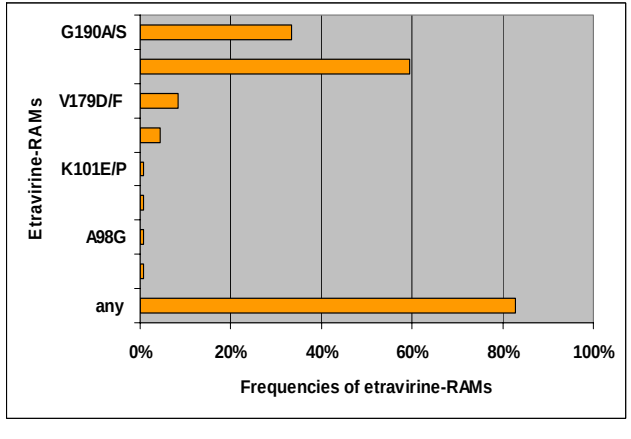

Table 1. Characteristics of patients with <3 and ≥3 etravirine-RAMs

Characteristics	Number of etravirine-RAMs		P value
	<3 (n=119)	≥3 (n=39)	
Male gender, number (%)	77 (65)	26 (67)	0.938
Age, mean (SD), years	36.0 (5.4)	36.5 (7.1)	0.865
Duration of ART, median (IDR), months	21 (13-39)	20 (12-29)	0.680
Prior ART regimen			
- NRTIs backbone:			0.579
d4T + 3TC	107	36	
AZT + 3TC	2	1	
AZT + ddI	10	2	
- NNRTI:			0.241
Nevirapine	101	30	
Efavirenz	18	9	
CD4 cell counts at virological failure, median (IQR), cells/mm^3	182 (132-263)	173 (98-262)	0.889
HIV RNA at virological failure, median (IQR), log copies/mL	4.2 (4.6-4.9)	4.1 (3.7-4.7)	0.621

CONCLUSIONS

In resource-limited setting, three-fourths of patients who fail an initial NNRTI-based ART regimen can use etravirine in the second-line regimen. Unfortunately, genotype testing is needed to identify this group. Three-fourths of these patients, indicated by genotype results, may be able to use etravirine plus 2 active NRTIs for the second regimen. This strategy may be an option for HIV-infected patients who cannot afford or cannot tolerate protease inhibitor. Prospective study to evaluate this strategy should be conducted in resource-limited setting.