GENOTIPIC RESISTANCE PROFILE IN TREATMENT EXPERIENCED HIV-INFECTED INDIVIDUALS AFTER ABACAVIR AND EFAVIRENZ SALVAGE REGIMEN

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The risk of failure of highly active antiretroviral therapy (HAART) is particularly high in patients who have been pre-treated with nucleoside reverse transcriptase inhibitors (NRTI). Therapy failure may be defined as an insufficient decrease, increase or rebound of viral load and/or a decrease of CD4 cell count and/or an HIV-associated disease occurring during HAART. A probability of up to 40% has been reported for viral rebound in the first 2 years in pre-treated patients. Specific risk factors such as a low CD4 cell count and a high viral load could also contribute to virological failure. Unfortunately, the potential for cross-resistance to other protease inhibitors (PI) and NRTI is high in these patients, which makes difficult to find an effective alternative. Although the use of resistance testing is recommended in the setting of antiretroviral failure, it is not clear how to use genotype or phenotype to select a regimen for treatment-experienced patients.

The objective of this work was to examine whether heavily pre-treated patients with viral failure respond to a salvage therapy with abacavir (NRTI), efavirenz (NNRTI) and other antiretroviral drug.

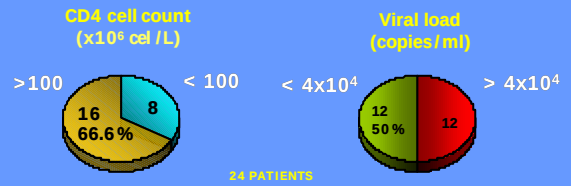
The study population included 24 heavily pre-treated patients with HAART failure who switched to a combination of abacavir, efavirenz, and either a NRTI (stavudine D4T, lamivudine 3TC or zidovudine ZDV) or a PI (nelfinavir NFV, ritonavir RTV or indinavir IDV) in a retrospective analysis. All patients were naïve to abacavir and efavirenz and had been heavily pre-treated with a variety of antiretroviral drugs, including PIs, NRTIs and NNRTIs.

METHODS

All patients were monitored for 24 weeks and analysed for CD4 cell counts, HIV-RNA levels, and RT and protease resistance profiles. Most of them (83.3%) had been pre-treated with a variety of antiretroviral drugs for more than 8 years with a median number of therapy changes of 4 (range, 3 to 7).

RESULTS

Patient characteristics at baseline



Patient characteristics after 24 weeks

CD4 cell count (x10⁶ cel /L)

Increase >30 %	Stable	Decrease >30 %
8 (33.33%)	10 (41.66%)	6 (25%)

Viral load

Decrease >0.5 log	Decrease <0.5 log	Increase
6 (25%)	7 (29.16%)	11 (45.83%)

Resistance profile at baseline and after salvage regimen

Resistance to	Mutation	At baseline	After treatment
NRTI	41L	11 (45.8%)	13 (54%)
	69D/N	3 (12%)	3 (12%)
	69ins	1 (4%)	1 (4%)
	70R	2 (8%)	4 (16%)
	74V/I	3 (12%)	4 (16%)
	151M	2 (8%)	1 (4%)
	215Y/C	14 (58%)	11 (45.8%)
	219E	7 (29%)	6 (25%)
	None	3 (12%)	2 (8%)
NNRTI	98G	3 (12%)	3 (12%)
	103N	9 (37%)	10 (41%)
	181C	18 (75%)	15 (62%)
	190A	6 (25%)	14 (58%)
	None	3 (12%)	4 (16%)
PI	30N	3 (12%)	3 (12%)
	46L	6 (25%)	4 (16%)
	82A	5 (20%)	4 (16%)
	84V	3 (12%)	2 (8%)
	90M	14 (58%)	13 (54%)
	None	7 (29%)	7 (29%)

In the **protease gene**, 11 patients (45.8%) demonstrated at least two mutations at positions 30, 46, 48, 82, 84, 88, and 90 in the protease gene. A similar proportion of resistance mutations were found after 24 weeks.

In the **RT gene**, the Q151M mutation, which confers high-level resistance to abacavir and other NRTIs, was found in two patients (8.3%), and the T69SSG insertion was found in one patient (4.16%) at baseline. Other resistance-associated mutations were also found at positions 65, 74, 184, and 215. The most common high level resistance mutations for NNRTIs were K103N and Y181C. The G190A/S mutation, which confers high level resistance to efavirenz and nevirapine, was found in 6 patients (25%) at baseline and in 14 patients (58.3%) after the treatment, which suggests that this mutation is generated quickly during this treatment.

On the other hand, it is noteworthy that onepatient had no mutations in the known resistance positions at baseline and after 24 weeks in spite of strict adherence to the treatment regimen. No RT-associated mutations were found in two patients, and no PI-associated mutations were found in four patients.

CONCLUSSION

- Since all patients were heavily pre-treated it is not surprising that many resistance-associated mutations were found at baseline.
- Abacavir and efavirenz showed a limited virological activity in pre-treated patients.
- This therapy stabilized or enhanced the immunological response in 75% of the patients, and decreased viral load in 54% of patients, which is beneficial when newer compounds are not yet available or when other regimens are not applicable because of poor adherence or serious side-effects.
- These results also showed that drug resistance mutations are very prevalent among heavily pre-treated patients who failed several regimens. A lower level of plasma HIV-RNA seems to have had no effect on the evolution of mutations in these patients.

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