Evolution of drug resistance in HIV infected patients remaining on a virologically failing cART regimen

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BACKGROUND

HIV treatment guidelines recommend that after confirmed virological failure a new regimen containing ≥3 expected to be virologically active and tolerated drugs is started. However, in everyday clinical practice, it may happen that patients with limited therapeutic options and a low level viral rebound (for example with a viral load<10,000 copies/mL) are kept on a virologically failing regimen probably due to perceived short-term virological and immunological benefit or other personal decisions. This strategy, for example, has the advantage of assuring a good adherence to the regimen as patients have already shown to tolerate the virologically failing regimen while it is uncertain that the new regimen will be accepted the same way. However, there is a main risk associated with this strategy: the accumulation of HIV drug resistance.
Nevertheless, the extent of drug resistance accumulation and the consequent risk of loss of future drug options in such patients remains unclear.

OBJECTIVES

- To describe the extent of drug resistance accumulation for a given regimen in patients with persistent viral load>400 copies/mL and its possible impact on loss of future options.
- To identify the predictors of resistance accumulation

METHODS

Among all patients of EuroSIDA with genotypic data available we studied all 110 people who fulfilled the following: had two genotypic tests performed at 2 time points (t0 and t1) over a period when viral load was >400 copies/mL and the regimen was unchanged (failing regimen containing ≥3 drugs). All data were obtained from retrospective sequencing of stored samples. Sequence analysis of HIV-1 PR and RT reading frames was performed using the Trugene HIV-1 Genotyping Kit and OpenGene DNA Sequencing System (version 8.0) according to the manufacturer's recommendations.

Assumption: drug resistance mutations (DRM) present at t0 were assumed to be still present at t1. DRM were those listed in the IAS document of April 2005 (www.iasusa.org).
We described the prevalence of DRM at t0 and the incidence of acquired mutations between t0 and t1. We also described mean values (and changes between t0 and t1) in the following parameters:
total number of IAS-DRM, total number of amino-acid differences from HXB2 strain, genotypic sensitivity score of failing regimen (GSS_f, giving a score of 0 if virus is resistant to drug in failing regimen, 0.5 if intermediate and 1 if sensitive), GSS of a virtual regimen containing all licensed drugs available today (GSS_t – same scores as above but using all drugs), viral load and CD_4 count. GSS_f and GSS_t were calculated using the Rega interpretation system (IS version 6.3). NB: the GSS_t is not representative of the real options that patients had at the time of analysis because some of the drugs available today were not licensed then.

Statistical analysis

Mean (SD) changes of the parameters between t0 and t1 were calculated. A linear regression analysis with the primary outcome time adjusted change in GSS_t between t1 and t0 was performed.
Other time adjusted endpoints expressing HIV evolution between t0 and t1 were also used. The following covariates were considered:
age, gender, ethnicity, mode of HIV transmission, viral load pre-ART, viral load at t0, CD_4 count nadir, CD_4 count at t0, previous duration of exposure to cART and current failing regimen, total number of drugs previously used, number of drug classes previously failed, type of failing regimen (single PI, ritonavir boosted PI, NNRTI, NRTI only, other combinations), presence of 184V at t0 and presence of lamivudine in failing regimen.

RESULTS

The main characteristics of the study population at t0 are shown in Table 1.Despite the fact that patients were not heavily pre-treated, on average, at t0 only 1.1 drugs in the failing regimen were still active against their virus population according to Rega IS. Specifically, at t0, n=20 patients (18%) had a GSS_f=0, 57 (52%) had a GSS_f of 0.5-1.5 and 33 (30%) had a GSS_f ≥2.
The median time between t0 and t1 was 6 months (range: 2-28).
Seventy-five percent of the viral load values measured at t0 or t1 were in the 400-50,000 copies/mL range.
The median calendar year at t0 was 1998 (range: 1996-2001).

In the majority of patients the failing regimen was a treatment containing more than three drugs belonging to NRTI, NNRTI and PI classes ("other combinations", Figure 1).
Most of the patients were receiving PI-based therapies (Figure 1).

HIV drug resistance mutations

The prevalence of drug resistance at t0 was relatively high: the percentage of people with TAMs was 74.6% (n=82), 76.4% (n=84) with 184V, 19.1% (n=21) with ≥1 NNRTI-associated mutation, 58.2% (n=64) with ≥1 major PI mutations and 89.1% (n=98) with ≥1 minor PI mutations.

Seventy-seven percent of patients (85 out of 110) acquired ≥1 IAS mutation over t0-t1 that was not already present at t0; 27 acquired ≥1 TAM, (24.6%), 7 acquired 184V (6.4%), 13 ≥1 NNRTI mutations (11.8%), 40 ≥1major PI mutations (36.4%) and 51 ≥1minor PI mutations (46.4%) (Figures 2a/b).

Mean CD_4 count remained stable around 280 cell/μl over t0-t1 (crude estimate of 6 monthly change: -9.79 cells/μl, SD: 113.5, p-value against mean=0, p=0.39) in spite of a small increase in viral load (+0.14 $\log_{10}$ copies/ml, SD: 0.91, p=0.14). Accumulation of DRM was inversely related to the prevalence of resistance to the failing regimen present at t0, those with lower prevalence showing greater accumulation.
The opposite trend was observed for the accumulation of all amino-acid changes from HXB2 (Table 2).

Predictors of HIV genetic evolution

In the model with the primary outcome change in GSS_t per 6 months, GSS_f at t0 was the only significant predictor. The adjusted differences in change, compared to patients with GSS_f ≥2 (group C), were +1.28 (95% CI:+0.14; +2.41, p=0.03) for group A (GSS_f=0) and +0.33 (95% CI:-0.54; +1.20, p=0.46) for group B (GSS_f of 0.5-1.5). This effect was also observed for the outcome "number of IAS-DRM" although none of the differences were significant: -0.80 (A vs. C, 95% CI: -2.56; +0.97, p=0.37) and +0.03 (B vs. C, 95% CI:-1.23; +0.97, p=0.96). Similarly for the third outcome "number of changes from HXB2", adjusted differences were not significant: +6.94 (A vs. C, 95% CI: -8.11; +21.99, p=0.36) and +3.78 (B vs. C, 95% CI:-6.89; +14.45, p=0.48). In this last model, a greater change in CD_4 count at t0 from nadir was independently associated with greater HIV genetic evolution (+3.25, 95% CI:+1.31; +5.19 p=0.001). Results of this third outcome were driven by the number of non–IAS changes (data not shown).

CONCLUSIONS

In patients kept on the same virologically failing cART regimen (>400 copies/mL) for a median of 6 months, there was considerable accumulation of DRM. The loss of potential virologically active drugs for future options is likely to be the smallest in people with extensive resistance to the failing regimen and the greatest in those with little resistance.
Interestingly, however, group A (GSS_f =0 at t0) tended to accumulate the largest number of amino-acid changes from HXB2.

Table 1

Characteristics of study population at t0 (n=110)

Age, years – median (range)	39 (21-70)
Female, n (%)	15 (13.6%)
Homosexual , n (%)	54 (49.1%)
Heterosexual , n (%)	24 (21.8%)
IDU , n (%)	22 (20.0%)
Other , n (%)	10 (9.1%)
Number of drugs previously used – median (range)	5 (3-10)
Number of drug classes previously failed (6 months with VL>400) n (%)	
1	31 (20.9%)
2	70 (63.6%)
3	8 (7.3%)
Months of ART – median (range)	45 (6-136)
Months of cART – median (range)	13 (6-58)

Figure 1

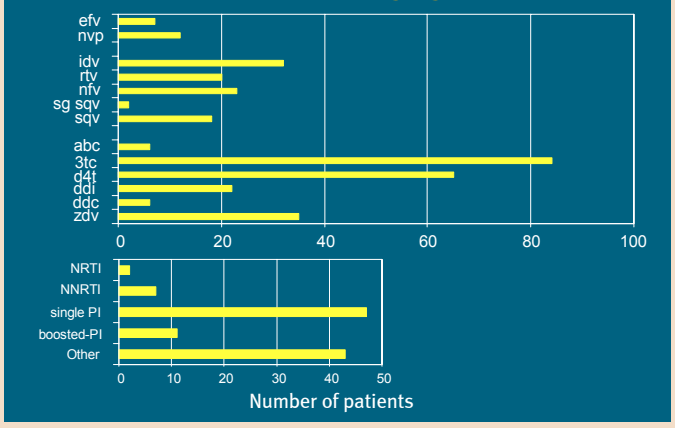

Figure 2a

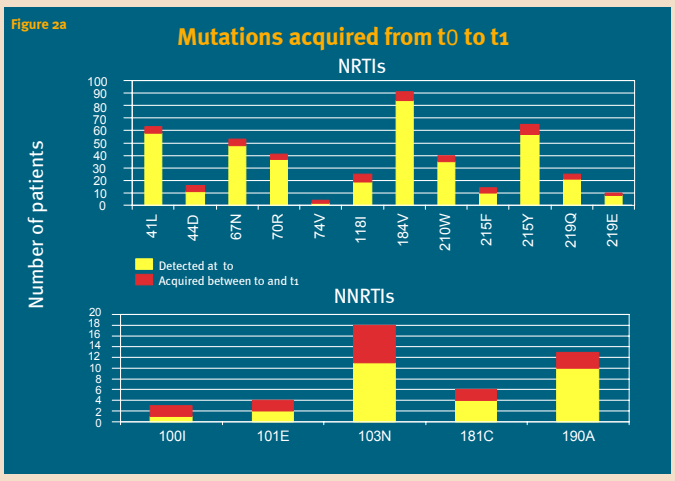

Figure 2b

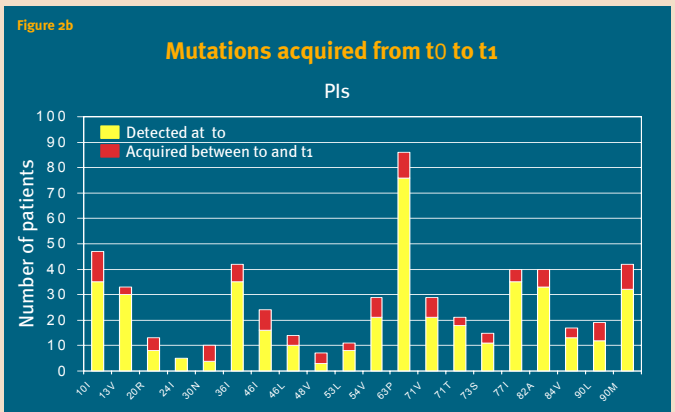

Table 2

Changes between t0 and t1

GSS_f (t0)		Crude Mean (SD) t0	Crude Mean (SD) t1	Crude change t1-to per 6 months (SD)
			GSS_t	
A	0	8.22 (2.71)	7.66 (3.00)	-0.60 (1.05)
B	0.5-1.5	11.48 (3.70)	10.13 (3.96)	-1.27 (1.93)
C	≥ 2	15.60 (1.89)	13.64 (2.81)	-1.78 (1.90)
			Number of IAS-DRM	
A	0	12.00 (3.66)	13.36 (4.08)	+1.43 (1.71)
B	0.5-1.5	8.29 (4.65)	10.33 (5.13)	+2.07 (2.34)
C	≥ 2	3.56 (2.47)	5.80 (2.90)	+2.13 (2.34)
			Number of changes from HXB2	
A	0	43.91 (30.63)	75.14 (33.81)	+36.82 (21.71)
B	0.5-1.5	35.14 (24.08)	60.87 (28.24)	+30.22 (23.43)
C	≥ 2	23.64 (10.72)	43.88 (11.33)	+17.78 (8.92)

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