Poster 72

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Rate of accumulation of thymidine analogue mutations in patients left on virologically failing regimens containing zidovudine or stavudine

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BACKGROUND

The WHO 2006 guidelines suggest that, in resource-limited settings without access to HIV-RNA monitoring, antiretroviral therapy (ART) should be switched when patients experience immunological/clinical failure. Such a strategy will result in a substantial number of patients being maintained for extended periods on a virologically failing thymidine analogue (TA) containing regimen. Estimates of the potential consequences of such a delayed switch of ART - in terms of accumulation of TA mutations (TAM) - are needed.

OBJECTIVES

To estimate the rate of TAM accumulation and to identify groups of patients who are more likely to accumulate TAM when kept on zdv- or d4t-based therapies despite virological failure.

STUDY DESIGN - METHODS

Patients: patients of EuroSIDA with ≥2 available genotypic resistance test (GRT) (HIV RNA had to be >500 cps/mL at the time of the test and in between tests) provided the first GRT was after the date of first virological failure of zidovudine (zdv) or stavudine (d4t) and that the TA was kept until the time of the 2nd GRT (other drugs could be changed). The statistical unit was pairs of GRT and patients with j GRT (j≥2) contributed j-1 pairs (e.g. a patient with 4 eligible genotype tests contributed 3 pairs, a patient with 3 eligible genotype tests contributed 2 pairs, etc.). Figure 1 illustrates a typical patient included in this analysis and contributing 2 pairs of genotypes while on a virologically failing zdv-containing regimen.

STATISTICAL ANALYSIS

Patients' characteristics at time of first GRT (to) were described and average changes in laboratory markers from to to t1 (time of 2nd GRT) were evaluated. The Rega interpretation system (IS version 6.4.1 for the main analysis and –limited to the analysis of NRTI cross resistance- version 7.1) was used to predict the number of active drugs in the ART regimen at to.

In this analysis, it was assumed that TAM identified at to was still present at t1. The rate of TAM accumulation was calculated as number of new TAM per person years of follow-up (PYFU). Analyses were repeated in patients with ≤3 TAM detected at first GRT and in those receiving only NNRTI besides zdv/d4t. A multivariable Poisson regression model was performed to identify independent predictors of TAM accumulation. The model properly accounted for the fact that a patient could contribute more than one pair of genotypes and that pairs coming from the same patients could not be assumed to be independent observations.

RESULTS

Main characteristics

We included 316 patents who contributed 501 pairs of GRT (219 one pair, 116 two, 57 three, 109 greater than three pairs, Table 1); Table 1 also includes a description of the main characteristics of the patients.

Laboratory markers

At to VL was 4.14 log (IQR: 3.52-4.80) and CD4 count 250 cells/µl (144-369). In 86 patients with a viral load measured before any ART was initiated (viral load set point), the median viral load suppression below this value at to was 0.79 log (0.16-1.38, Table 2). Over the interval to-t1 (median of 7 months) we observed a very stable viral load [mean change: +0.02 log copies/mL (95% CI:-0.04;+0.08)] and CD4 count [mean change:+5.85 cells/µl, 95% CI:-3.32;+15.02].

Antiretroviral drugs

For 153 pairs, the patient was on a zdv-, and for 348 on a d4t-containing regimen (Table 1). At first GRT in a pair, the median number of drugs in regimen was 3 (range:2-6) and the third drug -besides the zdv/d4t-containing nucleoside backbone- was abacavir (10%) a NNRTI (32%) a PI (53%) or a combinations of NNRTI and PI (37%). The most common 2nd NRTI were lamivudine (56%), didanosine (16%) and zalcitabine (3%). Tables 3/4 show the detailed distribution of drugs used at first (to) and second (t1) test of the pair.

HIV drug resistance

The median number of TAM at to was 3 (0-6); for 14% of the pairs, viruses were of intermediate resistance and for 28% susceptible to zdv/d4t (Rega IS). The median number of active drugs in the regimen (excluding zdv/d4t) was 0.5 (0-4, Rega IS). Table 4 shows the distribution of TAM detected in major virus populations at to and the estimated proportions at t1.

Figure 1

Typical patient contributing 2 genotypic test-pairs

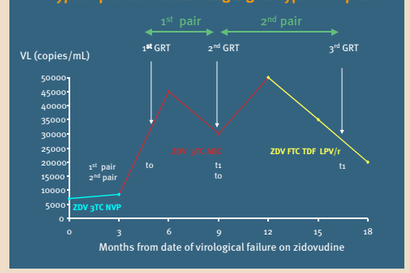

Table 1

Patients characteristics (n=316)

Age, median (IQR)	38 (34-45)
Female, n(%)	45 (14.2%)
Homosoexual contacts, n(%)	176 (55.7%)
Heterosexual contacts, n(%)	66 (20.9%)
IDUs, n(%)	43 (13.6%)
Number of contributing pairs	
1	219 (69.3%)
2	116 (36.7%)
3	57 (18,0%)
>3	109 (34.4%)

Table 2

Characteristics of genotype pairs (n=501)

	median (IQR)
Time from VF of zdv or d4t to to, months	19 (10-34)
Date of to	Mar 99 (Jan 98-Nov 00)
VL suppression < set-point, log cps/mL	0.79 (0.16;1.38)
VL at to, log copies/mL	4.15 (3.52;4.80)
CD4 count at to, cells/µl	250 (144;369)
Time between tests, months	7 (4-13)
Time on zdv-based regimens from VF to t1, months	13 (5-22)
Time on d4t-based regimens from VF to t1, months	13 (7-24)
	n (%)
Non-B HIV subtype	76 (15%)
zdv-based regimens	153 (31%)

VF=virological failure; to=time of 1st GRT, t1=time of 2nd GRT

Rate of accumulation of resistance

Overall, 118 TAM were accumulated over 500 PYFU (0.24 per year, 95% CI:0.19-0.28) and the rate was 0.31/year (95% CI: 0.25-0.38) in those with ≤3 TAM (102 new TAM over 327 PYFU). In patients whose third drug at to was a NNRTI we estimated an average accumulation 25 TAM over 81 PYFU (i.e., again, a rate of 0.31/year (95% CI:0.21;0.42). The following switches in predicted susceptibility of other NRTI from to to t1 were observed: S↗I (17% ddI, 22% abc, 15% tdf), S↗R (5% ddI, 4% abc, 1% tdf), I↗R (17% ddI, 16% abc, 9% tdf) as a consequence of acquired cross-resistance (Table 4).

Predictors of TAM accumulation

The rate of accumulation of TAM was 2-fold greater in patients who acquire HIV via heterosexual contacts (vs. homosexuals), 49% greater per each longer years spent on zdv with a VL>500 cps/mL and 54% greater per additional active drug in the regimen besides the thymidine analogues. The rate of accumulation was 26% slower per each TAM detected at to (Table 5). Results were similar when restricting the analysis to patients with 0-3 TAM at to, although the number of TAM detected at to was no longer predictive of the risk of TAM accumulation (ARR: 0.91, 95% CI: 0.67-1.26, p=0.58). In patients receiving NNRTI as the third drug at to, longer duration of exposure to zidovudine was the only significant predictor of TAM accumulation (ARR:2.51, 95% CI:1.35-4.67, p=0.004).

CONCLUSIONS

Patients who are kept on a virologically failing regimen containing a TA acquire new TAM at a relatively slow rate (on average, 1 additional TAM every 3.3 years of exposure to the regimen). As a consequence, on average, the activity of 0.1 NRTI that are candidate to be used as backbones of future second-line therapies was lost.

Patients at greater risk of TAM accumulation were those who acquired HIV via heterosexual contacts (vs. homosexuals), those who have long exposure to zidovudine-based regimens and those who at to had less predicted resistance to the other drugs in the regimen. In contrast, as expected, a larger number of TAM detected at to was associated with a slower rate of TAM accumulation.

Our data suggest that a combination of poor adherence and greater activity of the drugs in the regimen other than TA may have determined the greatest accumulation of TAM; although the estimated rate of TAM accumulation was maybe lower than anticipated, all possible efforts should be continued to increase the availability of drug options.

LIMITATIONS

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. We are currently performing an analysis to examine the extent to which viral load changes predict drug switches in these patients. However, because patients were allowed to switch drugs other than TA and viral load at to was not significantly associated with the rate of TAM accumulation, bias is unlikely to be important. The impact of resistance accumulation on the response to possible second-line regimens remains to be seen.

Only 15% of our patients had non-B subtypes and 50% were receiving antiretroviral drugs not currently available in developing countries. Therefore, our results mat not be fully generalised to the context of patients in these countries but should stimulate the conduct of similar analyses.

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Table 2

ARV used besides zdv/d4t

	to	t1
Didanosine	126 (25%)	140 (28%)
Lamivudine	351 (71%)	332 (66%)
Abacavir	71 (14%)	101 (20%)
Tenofovir	11 (2%)	23 (5%)
Nevirapine	148 (30%)	161 (32%)
Evafirenz	73 (15%)	90 (18%)
Saquinavir	73 (15%)	54 (11%)
Nelfinavir	107 (21%)	118 (24%)
Amprenavir	17 (3%)	22 (4%)
Lopinavir	43 (9%)	58 (12%)
Ritonavir	97 (19%)	97 (19%)
Indinavir	119 (24%)	102 (20%)
Atazanavir	2 (0.4%)	3 (0.6%)
Total	501 (100%)	501 (100%)

Table 4

TAM detected in major populations at to and estimates at t1 and cross resistance with other NRTI

	to	t1	change to-t1
TAM 1			
41L	304 (61%)	328 (65%)	
210W	214 (43%)	244 (49%)	
215Y	311 (62%)	335 (67%)	
TAM 2			
67G	23 (5%)	30 (6%)	
67N	243 (49%)	262 (52%)	
70R	175 (35%)	185 (37%)	
215F	97 (19%)	120 (24%)	
219E	53 (11%)	59 (12%)	
219H	4 (1%)	6 (1%)	
219N	29 (6%)	37 (7%)	
219Q	108 (22%)	114 (23%)	
219R	21 (4%)	28 (6%)	
GSS ABC/ddI, mean (SD)	0.85 (0.78)	0.72 (0.74)	-0.13 (0.31)
GSS ABC/TDF, mean (SD)	1.00 (0.74)	0.89 (0.72)	-0.11 (0.29)
GSS TDF/ddI, mean (SD)	1.05 (0.76)	0.94 (0.74)	-0.12 (0.31)

Table 5

Adjusted relative rate of accumulation of TAM from fitting a Poisson regression model

Factor	ARR (95% CI)	p-value
Homosexual contacts	1.00	
Heterosexual contacts	2.07 (1.14-3.78)	0.02
Years on zdv with VL500 (per 1 longer)	1.49 (1.22-1.82)	0.0001
GSS (drugs besides zdv/d4t) (per one additional active drug)	1.54 (1.11-2.15)	0.01
Number of TAM at to (per 1 more mutation)	0.74 (0.60-0.92)	0.007

Also adjusted for: age, gender, years on d4t with VL500, number of drugs failed prior to to, whether zdv/d4t active according to Rega IS, viral load at to, CD4 at to, 184V detected at to, total number of drugs received at to, and whether lamivudine was received at to.

CHIP COPENHAGEN HIV PROGRAMME

EuroSIDA