BACKGROUND

The WHO 2004 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 would result in a substantial number of patients being maintained on extended periods on a virologically failing thymidine analogue (TA) containing regimens. Estimates of the potential consequences of such a delayed switch of ART - in terms of accumulation of TAM 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 or during-based therapies despite immunological failure.

STUDY DESIGN - METHODS

Patients: patients of EuroSIDA with (a) available genotypic resistance test (GRT) (HIV RNA load ≥ 1000 copies/ml at the time of ART was started and between tests) and (b) the first GRT was after the last time of virological failure of stavudine (ZDV) or stavudine/nicotinamide (ZDVN) and that the TAM was kept up to the time of the 2nd GRT (other drugs could be changed). The statistical unit was patients of GRTs and with TAM (≥ 1 pairs) contributed 1 pair, e.g. a patient with ≥ 3 TAM genotypic tests contributed ≥ 3 pairs, a patient with ≥ 3 TAM genotypic tests contributed ≥ 2 pairs, etc. Figure 1 illustrates a typical patient included in this analysis and contributes ≥ 2 pairs of genotypes while on a virologically failing zidovudine-containing regimen.

STATISTICAL ANALYSIS

Patients’ characteristics at time of first GRT (to) and average changes in laboratory markers from to to time of second GRT (t1) 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 2.0 was used to predict the number of active drugs in the ART regimen to to.

In this analysis, it was assumed that TAM identified at t0 was still present at t1. The rate of TAM accumulation was calculated as a number of new TAM per person years of follow-up (PY:PS). Analyses were repeated in patients with ≥ 2 TAM detected at first GRT and in those receiving only NRTI besides ZDV/3TC. A multivariable 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 used to independent observations.

RESULTS

Characteristics of genotypic pairs (n=501)

- Patients’ characteristics at time of first GRT (t0) were described and average changes in laboratory markers from t0 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 2.0 was used to predict the number of active drugs in the ART regimen to t0.

A very stable viral load [mean change: +0.02 log copies/ml 95% CI:-3.32;+15.02] was observed over the interval t0-t1 (median of 7 months) (Table 2).

CONCLUSIONS

Patients who are kept on a virologically failing regimen containing a TA accumulate more TAM at a relatively slow rate (on average, 1 TAM every 3 years of exposure to the regimen). As a consequence, on average, the activity of a TAM that fits to be used as backbone of future second-line therapies was lost.

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 zidovudine, it is not significantly associated with the rate of TAM accumulation, bias is likely to be important. The impact of resistance accumulation on the response to possible second-line regimens remains to be seen.

Table 3 shows the distribution of TAM detected in major virus populations at the to and estimated proportions at t1.

Table 4 shows the distribution of TAM detected in major virus populations at t0 and the estimated proportions at t1.

Table 5 shows the distribution of TAM detected in major virus populations at t0 and the estimated proportions at t1.

Table 6 shows the distribution of TAM detected in major virus populations at t0 and the estimated proportions at t1.

Table 7 shows the distribution of TAM detected in major virus populations at t0 and the estimated proportions at t1.

Table 8 shows the distribution of TAM detected in major virus populations at t0 and the estimated proportions at t1.

Table 9 shows the distribution of TAM detected in major virus populations at t0 and the estimated proportions at t1.

Table 10 shows the distribution of TAM detected in major virus populations at t0 and the estimated proportions at t1.

Table 11 shows the distribution of TAM detected in major virus populations at t0 and the estimated proportions at t1.

Table 12 shows the distribution of TAM detected in major virus populations at t0 and the estimated proportions at t1.

Table 13 shows the distribution of TAM detected in major virus populations at t0 and the estimated proportions at t1.

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