Thymidine Analogue Mutation Profiles: Factors Associated with Acquiring Specific Profiles and Their Effect on Virologic Response to Therapy

A Cozzi-Leprini, L Ruiz, C Lovieda, AN Phillips, B Cloet, P Reiss, and JF Lundgren for the EUROSIDA Study Group

Royal Free and University College Medical School, London, UK.

BACKGROUND

Small studies have suggested that HIV-1 evolves TAMs by one of five distinct pathways defined as TAM1, TAM2, TAM3, TAM4, and TAM5.

METHODS

Study Population

We considered the first chronologically genetic test result obtained as TAMs in the EuroSIDA database.

Sequencing

HIV-1 RNA levels were determined from patient blood plasma using QNUNI kit according to manufacturer's instructions. Sequence analysis of HIV-1 and RT activity tests were performed using the Trugene HIV-1 Genotyping Kit and OpenGene DNA Sequencing System following the manufacturer's recommendations.

Statistical analysis

The factors associated with carrying a TAM profile (i.e., carrying a TAM profile were investigated using a logistic regression analysis. Numbers and viral load reductions were compared using a linear regression analysis for confirmed data (due to some viral load values at 6 months being below the lower limit of the assay).

RESULTS

Study Population

We originally included 733 patients with a genetic sequence in which one or more TAMs had been detected.

TAM Clustering

Table 1 compares the observed probabilities of falling into TAM/TAM profiles with those that could be expected to occur by chance alone for a fixed number of TAMs of 2. Thus, for instance, since the TAMs up to a total number of 2 we are considering the mutations 41L, 210W, 215Y, 67N, 70R, 219E and 219Q and the remaining 31 mixed profiles. For instance, this would be expected by chance alone and which were classified as one TAM or multiple TAMs (including 41L with a single TAM or 41L with a single TAM) were classified as one TAM or multiple TAMs (including 41L with a single TAM or multiple TAMs) were not further analyzed.

TAM Clustering

Table 1 compares the observed probabilities of falling into TAM/TAM profiles with those that could be expected to occur by chance alone for a fixed number of TAMs of 2 or 3. Thus, for instance, since the TAMs up to a total number of 2 we are considering the mutations 41L, 210W, 215Y, 67N, 70R, 219E and 219Q and given that 219E and 219Q cannot be detected simultaneously, 30 possible triplets including these mutations can be constructed (e.g., 5: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13). Of these one would be of type TAM1 (4L, 210W, 215Y); two of type TAM2 (41L, 210W, 215Y), and the remaining 27 mixed profiles. For instance, this would be expected by chance alone and that, in contrast, the mixed profiles should have occurred more frequently if the suggested clustering was not a real phenomenon.

CONCLUSIONS

This study provides evidence that the suggested TAM clustering is a real phenomenon and, most importantly, suggests that clustering TAMs, may still be active against TAM-resistant viruses. The interpretation of our results is limited by the fact that the allocation of zidovudine and stavudine was confounding due to lack of randomisation cannot be ruled out.