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AZT RESISTANCE: A CASE-CONTROL STUDY IN THE CONCORDE TRIAL

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OBJECTIVES: To evaluate in patients on Concorde trial a possible correlation between AZT resistance with clinical progression, changes in CD4 counts and RNA viral load.

Patients: 28 progressors (18 AIDS, 10 ARC) were matched with 31 non-progressors for time on AZT (mean : 533d.), entry CD4 cell number (mean:425/ μ l) and p24 antigenemia status at the enrolment. Specimens: Three to five stored specimens per patient were studied: pretreatment, at months 3 and 6, then at the time of the clinical event \pm 3 m. (mean: 533 \pm 231d.) and 6-9 m. before the clinical event (mean: 375 \pm 212d.).

METHODS: The *in vitro* sensitivity of the isolates (IC₅₀, IC₉₀) was determined by a PBMC-RT based assay. Mutations at codons 41,67,70, 215, 219 were detected by selective PCR on DNA extracted from PBL or cultured lymphocytes. The RT coding region was sequenced in selected cases. Using in-house methods developed in R. Tedder's laboratory, serum HIV-1 RNA was quantified by an immunocapture PCR, and genomic resistance in the same RNA was quantified by a point mutation assay (PMA).

RESULTS: High level of resistance (IC₅₀ \geq 1 μ M) was a rare event in these patients. Mutation at codon 215 was systematically associated with decrease in AZT susceptibility (IC₅₀ \geq 0.05 μ M). Single mutation at codon 70 was very common, not predictive of occurrence of resistance and could be observed in pretherapy specimens. The analysis of this case-control study, based on the PCR results, showed a significant association ($p=0.001$) between emergence of mutation at codon 215 and clinical

progression. Resistant viral populations were detected at least 6-9 months before the clinical event. Statistical analyses of the correlation between AZT resistance and clinical progression, adjusted on CD4 cell counts and viral load will be presented.

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