

M184V resistance mutation: back to the future?

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INTRODUCTION

With the extension of life expectancy of the patient living with the human immunodeficiency virus (PLHIV), characterization of the resistance-associated mutations (RAMs) and optimization of the ART are a key challenge considering their resistance and toxicities past histories. Several works using ultra deep sequencing (UDS) have demonstrated the decrease in the proportion of viral variants harbouring RAMs in the HIV reservoir over time in PLHIV with sustained viral suppression. The M184V RAM induced a strong level of resistance of two well used ART, Emtricitabine (FTC) and Lamivudine (3TC). Moreover, ART treatment, including FTC or 3TC are the most currently recommended by the antiretroviral treatment guidelines that reinforces the interest of the possible recycling of these molecules.

➡ The aim of this study was to characterize the precise kinetics of the M184V mutation decrease in proviral DNA, to establish a predictive model of M184V mutation clearance over time.

METHODS

To characterize the kinetic of the M184V clearance in HIV reservoir :

- We selected 25 HIV infected treated patients, receiving care at the Pitié-Salpêtrière hospital, virally suppressed (HIV RNA <50 copies/ml) for at least 5 years, with in all cases, the M184V resistance mutation documented in past genotypes.
- Sanger sequencing and UDS was performed from HIV-DNA from frozen blood samples at least one time/per year over 5 years to quantify the proportion of M184V-positive quasispecies. For the UDS, the sequence reads were analysed with a minimum coverage set at 50 and an ambiguity filter at 5% or at 2%. A Kaplan-Meier survival model was used to represent results.

RESULTS

The 25 HIV patients were 19 male and 6 female, with a median age of 56 years [49-65] and with a duration of virological suppression median (HIV-RNA < 50 copies/ml) of 8 years [6.9-10.4]. They present a median CD4 cell count of 579/mm³ [478-779] at the first time-point, a median NADIR of 180/mm³ [67-267] and a median HIV viral load zenith of 5.05 log₁₀ copies/ml [4.26-5.52].

- At the first time point, all the patients presented a M184V detected in the HIV reservoir.
- At 5 years, using an ambiguity filter at 2%, M184V mutation was no more detected in 64% of patients with a slope of decrease of -13.56% per year (Fig1A) and using 5% ambiguity filter, about 73% of patients with a slope of decrease of -15.01% per year (Fig1B).

Survival curve linear regressions predict that the M184V mutation will become undetectable in HIV-DNA of patients after at least 6.7 years using the <2% filter or 6.4 years using the <5% filter.

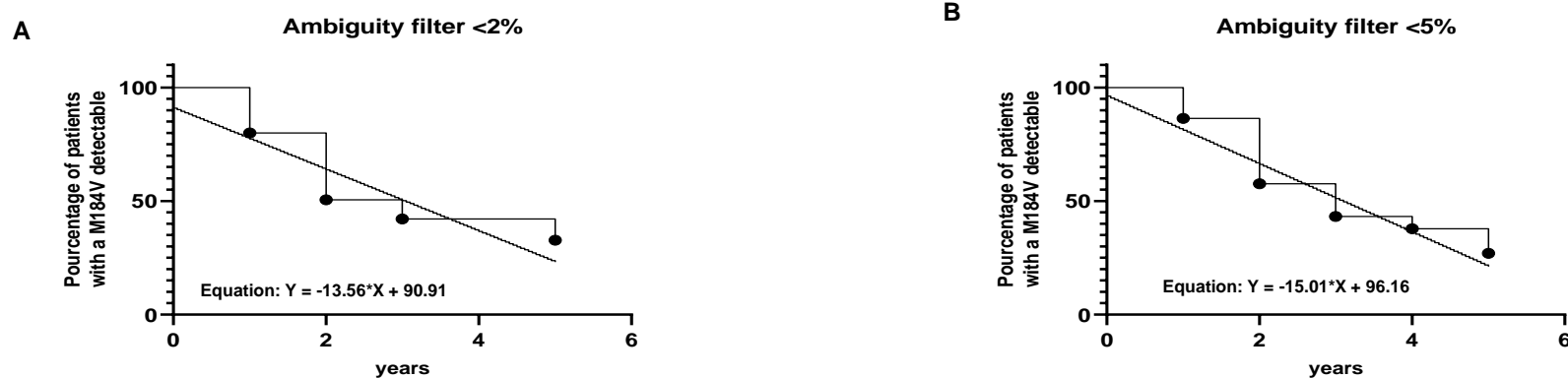


Figure 1. Clearance speed of the M184V mutation over time in HIV infected patients. Survival curves for the percentage of patients with a M184V detectable over time with an ambiguity filter at < 2% (A) or at <5% (B).

CONCLUSIONS

Our study provides new information concerning the clearance speed of M184V mutation over time in patients with fully suppressed viremia and open the discussion about duration needed to consider a 3TC/FTC recycling. Moreover, our results reinforce the fact that to evaluate the presence of RAMs quasispecies in order of ART recycling, the use of deep sequencing is preferable for DNA genotyping due to its better sensitivity. Indeed, the use of UDS increased the proportion of patients with detected RAMs compared to the Sanger sequencing, which failed to detect variants in less than 15%–25% of the total population.