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Evolution of the K65R, K103N and M184V/I reverse transcriptase mutations in HIV-1-infected patients experiencing virological failure between 2005 and 2010

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Objectives: To assess the prevalence of the K65R, K103N and M184V/I resistance mutations in the reverse transcriptase (RT) region in HIV-1-infected patients failing antiretroviral-based regimens between the years 2005 and 2010.

Patients and methods: HIV-1-infected patients experiencing virological failure between 2005 and 2010 with RT genotypic resistance tests available at the time of virological failure were analysed. K65R, K103N and M184V/I mutation frequencies were determined each year. Statistical analyses were performed using Fisher's exact test.

Results: Among 9586 patients failing their antiretroviral-based regimens from 2005 to 2010, the prevalence of K65R tended to decrease ($P=0.054$), while K103N and M184V/I mutation frequencies decreased significantly over time ($P<0.001$). The increased use of a tenofovir/emtricitabine/efavirenz single-tablet regimen was associated with decreased selection of these mutations.

Conclusions: The global prevalence of resistance-associated mutations to tenofovir, lamivudine/emtricitabine and efavirenz decreased over time between 2005 and 2010. Despite a stable rate of efavirenz and protease inhibitor use, this phenomenon can be explained by an increased use of single-tablet regimens, which simplify drug intake and maximize adherence.

Keywords: resistance prevalence, single-tablet regimens

Introduction

Combined antiretroviral-based therapy generally includes two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and a third agent that can be a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI) or an integrase inhibitor.[1]

Resistance selection at antiretroviral failure is one of the major issues that has to be taken into account and surveyed.[2] The rate of resistance selection at failure might be influenced by the drugs used, which could have different propensities for resistance selection, and their administered forms, such as fixed-dose combinations of two NRTIs and, more recently, three antiretroviral drugs together in a single tablet.

The objective of the study was to assess the prevalence of the K65R, K103N and M184V/I resistance mutations in the reverse transcriptase (RT) region in HIV-1-infected patients failing antiretroviral-based regimens between the years 2005 and 2010.

Patients and methods

In this retrospective longitudinal study we analysed HIV-1-infected patients experiencing virological failure between 2005 and 2010, whatever the antiretroviral regimen they were receiving, with an RT genotypic resistance test available at the time of virological failure. Virological failure was identified, as defined by French and European guidelines, by the occurrence of two consecutive HIV plasma viral loads >50 copies/mL in patients without any prior virological failure. RT genes were amplified and amplicons were submitted to direct sequencing according to the complete sequencing procedures and primers sequences, as described at www.hivfrenchresistance.org. The frequencies of K65R, K103N and

M184V/I resistance mutations were determined each year from 2005 to 2010. We also determined the frequencies of these mutations before (1 January 2005–30 April 2009) and after (1 May 2009–31 December 2010) the introduction in May 2009 of tenofovir/emtricitabine/efavirenz as a single-tablet regimen. Statistical analyses were performed using Fisher's exact test.

Results

The prevalence of K65R, K103N and M184V/I resistance mutations among the 9586 RT sequences obtained from antiretroviral-treated patients experiencing virological failure between 2005 and 2010 are depicted in Figure 1. The prevalence of the K65R resistance mutation tended to decrease, from 1.7% in 2005 to 1% in 2010 ($P=0.054$). The prevalence of both K103N and M184V/I resistance mutations decreased significantly over time: from 15.7% to 7.4% ($P<0.001$) and from 36.9% to 14.8% ($P<0.001$), respectively. A comparison of the prevalence of these resistance mutations before and after the introduction of tenofovir/emtricitabine/efavirenz as a single-tablet regimen in May 2009 in clinical practice was made. Significant decreases were observed for K65R, K103N and M184V/I [K65R from 1.3% to 0.6% ($P<0.001$), K103N from 10.6% to 4.7% ($P<0.001$) and M184V/I from 26.3% to 10.2% ($P<0.001$)] before and after May 2009, respectively.

Discussion

In the present study, we showed that the overall prevalence of resistance-associated mutations to tenofovir, lamivudine/emtricitabine and efavirenz decreased over time between 2005 and 2010 in antiretroviral-treated patients experiencing virological failure. Taking into account the analyses of antiretroviral use in patients treated in France between 2005 and 2010, we did not observe any increase in the prevalence of the K65R resistance mutation between 2005 and 2010, despite the use of tenofovir increasing from 30% to 59%. During this period the use of lamivudine in the regimen decreased from 63% in 2005 to 29% in 2010, while the use of emtricitabine increased from 8% in 2005 to 53% in 2010. The introduction and expansion of the use of efavirenz as a single-tablet regimen in May 2009 (tenofovir/emtricitabine/efavirenz) was associated with a decrease in the prevalence of the K103N resistance mutation as well as K65R and M184V/I, while the proportion of patients receiving efavirenz was stable during the same time (21.4% in 2005 and 21.8% in 2010). Moreover, the use of boosted PIs was also stable over time (57.5% in 2005 and 57.9% in 2010).

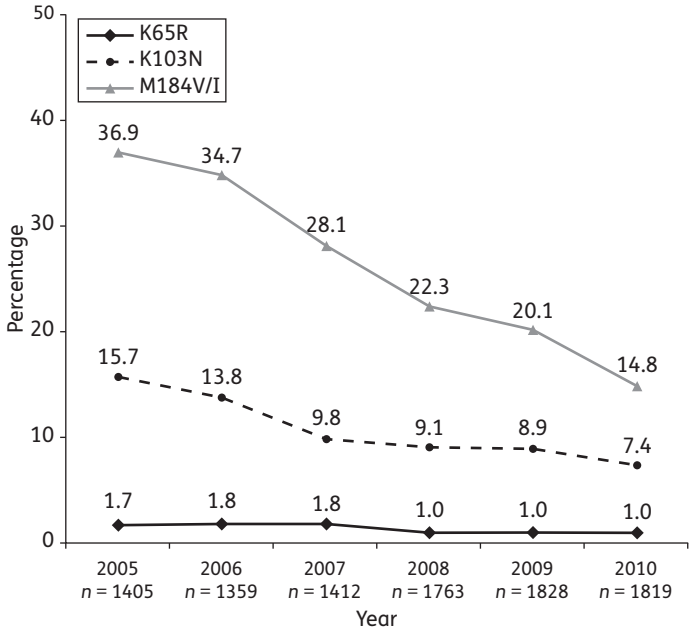

Figure 1. Percentage of K65R, K103N and M184V/I resistance mutations in antiretroviral-treated patients experiencing virological failure between 2005 and 2010. *n*, number of patients.

Differential adherence to components of combination antiretroviral therapy was previously reported as being common and associated with an increased risk of initial virological failure associated with antiretroviral drugs resistance.[3] With the use of once-daily single-tablet regimens, selective adherence is not possible, probably reducing the risk of resistance emergence, as we observed in our study. The use of once-daily single-tablet regimens has been associated with higher adherence and viral suppression than the use of multitablet regimens.[4]

The global prevalence of resistance-associated mutations to tenofovir, lamivudine/emtricitabine and efavirenz decreased over time between 2005 and 2010. Despite a stable rate of efavirenz and PI use, this phenomenon was statistically linked with an increased use of single-tablet regimens, which simplify drug intake and maximize adherence.

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Transparency declarations

None to declare.

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