Resistance profiles of emtricitabine and lamivudine in tenofovir-containing regimens

A. G. Marcelin1–3*, C. Charpentier4,5, M. Wirden1–3, R. Landman6, M. A. Valantin1,2,7, A. Simon8, C. Katlama1,2,7, P. Yeni6, D. Descamps4,5, C. Aubron-Olivier7 and V. Calvez1–3


*Corresponding author. Department of Virology, Pitie-Salpétrière Hospital, 83 Boulevard de l’Hôpital, 75013 Paris, France. Tel: +33-14-21-77-409; Fax: +33-14-21-77-411; E-mail: anne-genevieve.marcelin@psl.aphp.fr

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Objectives: To compare the frequency of the selection of the M184V/I resistance mutation in HIV-infected patients who experienced virological failure while receiving emtricitabine (FTC) or lamivudine (3TC), administered with tenofovir disoproxil fumarate (TDF) and either efavirenz (EFV) or a ritonavir-boosted protease inhibitor (PI; lopinavir or atazanavir).

Methods: Patient data held at two clinical centres in France were analysed retrospectively. Eligible patients had experienced virological suppression (plasma HIV RNA <200 copies/mL) for ≥6 months before experiencing their first virological failure (at least two measurements of plasma HIV RNA ≥200 copies/mL).

Results: Of the 880 patients eligible for the study, 278 patients had experienced virological failure while receiving FTC + TDF + ritonavir-boosted PI, 257 while receiving FTC + TDF + EFV, 178 while receiving 3TC + TDF + EFV and 167 while receiving 3TC + TDF + ritonavir-boosted PI. Proportions of patients harbouring the M184V/I mutation were 24% (n = 62) for those who received FTC + TDF + EFV versus 51% (n = 91) for 3TC + TDF + EFV (P = 0.0001; Fisher’s exact test); proportions were 11% (n = 30) for FTC + TDF + ritonavir-boosted PI versus 22% (n = 37) for 3TC + TDF + ritonavir-boosted PI (P = 0.002; Fisher’s exact test). The use of lamivudine versus emtricitabine (P = 0.001), non-nucleoside reverse transcriptase inhibitors versus ritonavir-boosted PIs (P = 0.01) and the level of viral load at the time of virological failure (P = 0.01) were associated with selection of the M184V/I mutation (logistic regression analysis).

Conclusions: Emtricitabine and lamivudine showed differing resistance profiles when administered in combination with tenofovir disoproxil fumarate and either efavirenz or a ritonavir-boosted PI. The prevalence of the M184V/I resistance mutation was significantly lower in patients who received emtricitabine and tenofovir disoproxil fumarate than in those who received lamivudine and tenofovir disoproxil fumarate.

Keywords: NTRIs, FTC, 3TC, HIV-1

Introduction

Treatment of HIV type 1 (HIV-1) infection with any combination of the antiretrovirals currently available is accompanied by the risk of development of viral resistance to the treatment regimen. For patients, the ultimate consequences of viral resistance to components of their antiretroviral regimen are rapid progression of HIV-1 infection and an increased risk of death.1–4 The characterization of factors that can minimize the risk of drug resistance is a key aspect of the development of long-lasting, effective treatment strategies.

Emtricitabine and lamivudine are two structurally related nucleoside reverse transcriptase inhibitors (NRTIs) that can be included in the initial treatment regimens of treatment-naïve patients in combination with another reverse transcriptase inhibitor and either a non-NRTI (NNRTI) such as efavirenz or a ritonavir-boosted protease inhibitor (PI).5,6 Both emtricitabine and lamivudine select for the methionine-to-valine/isoleucine
mutation in codon 184 (M184V/I) of HIV reverse transcriptase. M184V is one of the most common of the NRTI-associated mutations and results in a high level of resistance (>100-fold) to emtricitabine and lamivudine. Recent clinical studies comparing emtricitabine with lamivudine in terms of the development of the M184V mutation found lower rates of development of M184V for emtricitabine than for lamivudine in regimens containing the NRTI tenofovir disoproxil fumarate and in regimens including efavirenz. 

To provide data that may be useful in the identification of long-term, effective treatment regimens that possess a reduced risk of the development of viral resistance, we conducted an analysis to characterize the M184V/I resistance profiles of emtricitabine and lamivudine in patients who had experienced their first virological failure. The aim of the current analysis was to compare the frequency of selection of the M184V/I resistance mutation in groups of patients who had experienced virological failure while receiving emtricitabine or lamivudine, administered with the NRTI tenofovir disoproxil fumarate and either efavirenz or a ritonavir-boosted PI (lopinavir or atazanavir).

Materials and methods

This was a retrospective analysis of patient data held at two clinical centres in France: the Pitié-Salpêtrière Hospital, Paris and the Bichat Claude Bernard Hospital, Paris. Data for all patients were stored in a specifically designed anonymous database that included virological, demographic and therapeutic parameters.

Study population

Data were included in the analysis from patients who underwent successful antiretroviral therapy and achieved plasma HIV RNA concentrations ≤200 copies/mL for ≥6 months before experiencing their first virological failure. Virological failure was defined as at least two measurements of plasma HIV RNA ≥200 copies/mL. Most (~80%) patients underwent baseline genotypic assessment. For inclusion in the analysis patients had to be receiving one of the following treatment regimens: lamivudine/tenofovir/efavirenz (3TC+TDF+EFV), emtricitabine/tenofovir/efavirenz (FTC+TDF+EFV), lamivudine/tenofovir/ritonavir-boosted PI (3TC+TDF+PI/r) or emtricitabine/tenofovir/ritonavir-boosted PI (FTC+TDF+PI/r), where the ritonavir-boosted PI was either lopinavir or atazanavir. Patients receiving any other regimen were excluded from the analysis. All patients continued taking antiretroviral therapy.

Sample collection and HIV-1 sequence analysis

Patients provided blood samples on the occasion of their first virological failure (plasma HIV-1 RNA ≥200 copies/mL). Blood samples were drawn into tubes containing a suitable anticoagulant and plasma was isolated using a standard refrigerated centrifugation technique; plasma was stored at −20°C or lower until required. Reverse transcriptase and protease resistance genotypic analysis were conducted using plasma samples taken at the time of virological failure according to the Agence Nationale de Recherches sur le SIDA (ANRS) consensus method. Any sequences found to have a mixture of wild-type and mutant amino acid residues at single positions were considered to have the mutant at that position.

Plasma HIV-1 RNA concentrations and CD4 cell counts

Plasma HIV-1 RNA concentrations and CD4 cell counts were determined routinely for all patients as part of their continued care using techniques that were standard at the time the samples were taken.

Statistical analysis

Fisher’s exact test was used to compare the percentage of patients with treatment-emergent M184V/I between the treatment groups. Logistic regression was used to search for factors predictive of having an M184V/I mutation, including potential variables that provided a value of P<0.20 in the univariate analysis. Characteristics of patients were described using either frequency for categorical variables or median (IQR) for continuous variables. Fisher’s exact test and the Wilcoxon rank test were used to compare baseline characteristics of patients for categorical and continuous variables, respectively (level of significance, P<0.05).

Results

Patient disposition and treatment-related characteristics

Among 15,557 genotypic resistance testing results from patients who had experienced virological failure, we searched for patients receiving an emtricitabine/tenofovir- or lamivudine/tenofovir-containing regimen who had experienced virological failure for the first time; 880 patients were receiving one of the specific treatment regimens of interest (278 patients received FTC+TDF+EFV: proportion 257 received FTC+TDF+EFV, 178 received 3TC+TDF+EFV and 167 received 3TC+TDF+PI/r). All patients who received lopinavir or atazanavir received it in combination with low-dose ritonavir. One hundred and fifty (17%) patients were infected with HIV-1 non-B subtype. Overall, 48.8% of patients were receiving their first-line treatment at the time of their entry into the study and 51.2% were receiving at least their second-line treatment. There were no statistically significant differences between patients who received lamivudine/tenofovir or emtricitabine/tenofovir in terms of their demographic or treatment-related characteristics (Table 1).

Genotypic analysis

The prevalence of the M184V/I mutation was lower in patients who had experienced virological failure while receiving FTC+TDF+EFV than in those who received 3TC+TDF+EFV: proportions of patients were 24% (n=62) versus 51% (n=91); Figure 1. This difference achieved statistical significance (P<0.0001). In patients who received efavirenz, there was no statistically significant difference between emtricitabine/
Emtricitabine and lamivudine resistance profiles

Table 1. Demographic and treatment-related characteristics

<table>
<thead>
<tr>
<th></th>
<th>3TC + TDF (N=345)</th>
<th>FTC + TDF (N=535)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42 (35–52)</td>
<td>43 (39–51)</td>
<td>≥0.05</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>281 (75)</td>
<td>374 (70)</td>
<td>≥0.05</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>321 (190–480)</td>
<td>378 (180–512)</td>
<td>≥0.05</td>
</tr>
<tr>
<td>nadir</td>
<td>210 (145–273)</td>
<td>203 (150–203)</td>
<td>≥0.05</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (log copies/mL)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>4.2 (2.1–5.3)</td>
<td>4.1 (2.5–5.2)</td>
<td>≥0.05</td>
</tr>
<tr>
<td>Duration of last treatment before virological failure (weeks)</td>
<td>15 (6–29)</td>
<td>19 (10–31)</td>
<td>≥0.05</td>
</tr>
</tbody>
</table>

Values are median (IQR) unless otherwise indicated.

3TC, lamivudine; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine.

Figure 1. Proportions (%) of patients harbouring the M184V/I mutation. TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; EFV, efavirenz; 3TC, lamivudine; PI/r, ritonavir-boosted protease inhibitor.

In conclusion, this study adds to the body of evidence showing that emtricitabine and lamivudine exhibit differing resistance profiles when administered in combination with tenofovir and lamivudine/tenofovir in the proportions of patients with mutations denoting resistance to NNRTIs: proportions were 55% for those who received emtricitabine/tenofovir and 62% for lamivudine/tenofovir.

In patients who received a ritonavir-boosted PI, the proportion of patients harbouring the M184V/I mutation was lower in those who received emtricitabine/tenofovir than in those who received lamivudine/tenofovir: 11% (n = 30) versus 22% (n = 37). This difference achieved statistical significance (P=0.002). The proportion of patients who received a ritonavir-boosted PI and harbouring mutations denoting resistance to PIs was similar for the two treatments (6% for emtricitabine/tenofovir and 9% for lamivudine/tenofovir).

We searched for variables associated with the selection of the M184V/I mutation. The use of lamivudine versus emtricitabine (P=0.001), NNRTIs versus ritonavir-boosted PIs (P=0.01) and the level of viral load at the time of virological failure (P=0.01) were associated with selection of the M184V/I mutation.

Variables found to be not associated with M184V/I selection included baseline viral load level, HIV-1 subtype, baseline and nadir CD4 cell count and duration of virological failure.

Discussion

This study provided evidence of differences in the M184V/I resistance profiles of emtricitabine/tenofovir and lamivudine/tenofovir in patients experiencing virological failure for the first time. The prevalence of M184V/I was lower in patients who received emtricitabine/tenofovir than in those who received lamivudine/tenofovir. The differences between the two treatments achieved statistical significance and were evident whether the drugs were administered in combination with efavirenz or with a ritonavir-boosted PI. A statistically significant correlation was observed between the use of emtricitabine and a decreased probability of the emergence of M184V/I at the time of antiretroviral failure.

This study focused on patients receiving ritonavir-boosted lopinavir or atazanavir as the PI component of their treatment regimen. This was because these two PIs were the most widely prescribed at the time of study design and also because the number of patients taking other PIs in our database did not allow meaningful analysis.

The findings of this study were in line with those of two previous studies. In a study of 350 patients who received emtricitabine/tenofovir, lamivudine/tenofovir or lamivudine plus another NRTI, the lowest prevalence of the M184V mutation was found in patients treated with emtricitabine/tenofovir. In a second study, a retrospective evaluation of 859 patients from an Italian HIV resistance database found the emergence of the M184V, K70R, T215F and Y181C resistance mutations to be significantly more frequent in patients who received lamivudine/tenofovir than in those who received emtricitabine/tenofovir, independent of the third drug used in the treatment regimen (P<0.05).

The lower prevalence of M184V/I associated with the use of emtricitabine may be explained by the higher potency of emtricitabine than lamivudine, as suggested by previous in vitro and in vivo studies, and/or by the longer plasma and intracellular half-life of emtricitabine versus lamivudine. In addition, emtricitabine and tenofovir have a synergistic relationship in terms of anti-HIV-1 activity. This synergistic activity was compared with that of lamivudine/tenofovir in an in vitro study. Synergy levels for emtricitabine/tenofovir were found to be more than twice those of lamivudine/tenofovir (181.4 versus 80.4 μM²%).

The current study highlights the importance of identifying drug combinations that can minimize drug resistance. This is particularly relevant to resource-limited settings where there is limited access to viral load and genotypic resistance testing compared with developed countries. Therefore, the onset of genotypic resistance may go unseen for an unacceptably long period before it is identified. The identification of treatment regimens possessing a reduced likelihood of selecting resistance mutations may lead to more durable treatment options.

In conclusion, this study adds to the body of evidence showing that emtricitabine and lamivudine exhibit differing resistance profiles when administered in combination with...
tenofovir, favouring the combination of emtricitabine/tenofovir over lamivudine/tenofovir. There is a continued need for treatment strategies that demonstrate a lower tendency towards the development of resistance mutations. Such strategies will benefit patients whether they are able to access genotypic resistance testing readily or are in more restrictive, resource-limited settings where testing may take place on a less frequent basis.

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**Transparency declarations**

Conflicts of interest: none to declare.

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**References**


