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Short Communication

NRTI-sparing regimens yield higher rates of drug resistance than NRTI-based regimens for HIV-1 treatment

A.G. Marcelin [a,b,c,*], B. Visseaux [d,e], M. Wirden [a,b,c], L. Morand-Joubert [a,b,f], C. Soulie [a,b,c], C. Charpentier [d,e], B. Masquelier [g,h,i], D. Descamps [d,e], V. Calvez [a,b,c]

[a] Université Pierre et Marie Curie – Paris 6, UMR S-943, 75013 Paris, France
[b] INSERM, U943, 75013 Paris, France
[c] AP-HP Groupe Hospitalier Pitié-Salpêtrière, Laboratoire de Virologie, 75013 Paris, France
[d] Université Paris Diderot, Sorbonne Paris Cité, EA4409, 75018 Paris, France
[e] AP-HP Groupe Hospitalier Bichat-Claude Bernard, HUPNVS, Laboratoire de Virologie, 75018 Paris, France
[f] AP-HP Groupe Hospitalier Saint-Antoine, Laboratoire de Virologie, 75011 Paris, France
[g] Université de Bordeaux, Microbiologie Fondamentale et Pathogénicité, UMR 5234, 33000 Bordeaux, France
[h] CNRS, Microbiologie Fondamentale et Pathogénicité, UMR 5234, 33000 Bordeaux, France
[i] Laboratoire de Virologie, CHU de Bordeaux, 33000 Bordeaux, France

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ABSTRACT

To treat human immunodeficiency virus (HIV)-infected patients, international guidelines recommend the combination of two nucleos(t)ide reverse transcriptase inhibitors [N(t)RTIs] and a third agent [non-NRTI (NNRTI), boosted protease inhibitor (r/PI) or integrase inhibitor (INI)] for initial treatment. The objective of this study was to compare the selection of resistance to antiretrovirals (ARVs) for regimens containing or lacking N(t)RTIs in patients experiencing their first virological failure. Eligible patients had a first virological failure, defined as the occurrence of two consecutive HIV plasma viral loads ≥50 copies/mL. Genotypic resistance testing was performed at the time of virological failure (on the second sample with detectable viral load ≥50 copies/mL) in patients failing regimens of N(t)RTIs + r/PI or NNRTI or INI, r/PI + NNRTI or INI, and INI + NNRTI. Among 434 virological failures analysed, resistance testing results were available in 416 cases (95.9%). Higher rates of drug resistance were observed in patients receiving N(t)RTI-sparing regimens. When the combination of N(t)RTIs + r/PI was used, PIs protect themselves and the associated N(t)RTIs from the selection of resistance; however, this was not observed with the NNRTI + r/PI combination. The same phenomenon was observed for raltegravir: when used in combination with N(t)RTIs, INI resistance mutations were less frequently selected compared with its use in combination with PIs or NNRTIs. In conclusion, regimens of the ARV classes combined impact the frequency of resistance development. Lower resistance is observed for N(t)RTI-based regimens, with more therapeutic options for subsequent regimens after failure.

1. Introduction

Treatment of human immunodeficiency virus type 1 (HIV-1) infection with any combination of the antiretrovirals (ARVs) currently available is accompanied by the risk of virological failure and the development of viral resistance to the treatment regimen. For patients, the ultimate consequences of viral resistance to components of their ARV regimen are switching to more complicated regimens, progression of HIV-1 infection and an increased risk of death [1,2]. Characterisation of the factors or ARV combinations that can minimise the risk of drug resistance is one of the key aspects of the development of long-lasting effective treatment strategies.

To treat HIV-infected patients, international guidelines recommend the combination of two nucleos(t)ide reverse transcriptase inhibitors [N(t)RTIs] and a third agent [non-NRTI (NNRTI), boosted protease inhibitor (r/PI) or integrase inhibitor (INI)] for initial treatment. This is mainly based on arguments of potency and, for some of them, on the rate of resistance selection at failure. Indeed, data provided from clinical trials suggested that differences in terms of rate of resistance mutation selection are observed when N(t)RTI-containing versus N(t)RTI-sparing regimens were analysed [3–5]. These clinical trials showed that N(t)RTI-sparing regimens were more likely associated with resistance compared

* Corresponding author. Present address: Department of Virology, Pitié-Salpêtrière Hospital, 83 Boulevard de l'Hôpital, 75013 Paris, France. Tel.: +33 1 4217 7409; fax: +33 1 4217 7411.
E-mail address: anne-genevieve.marcelin@psl.aphp.fr (A.G. Marcelin).

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with N(t)RTI-containing regimens. For example, in the AIDS Clinical Trials Group A5142 and ANRS 121 trials, use of a NNRTI + r/PI regimen for the treatment of ARV-naïve patients was less successful than a N(t)RTI-based regimen and was associated with more resistance for NNRTIs and also for PIs [3,4].

To provide data in clinical practice that may be useful in the identification of long-term effective treatment regimens that possess a reduced risk of the development of viral resistance, an analysis was conducted to characterise the resistance profiles in patients who had experienced their first virological failure with different kinds of regimens that included or excluded N(t)RTIs.

The aim of the current analysis was to compare the prevalence of selection of resistance to ARVs for the drug classes of N(t)RTIs, NNRTIs, r/PIs and INIs in regimens containing or lacking N(t)RTIs in patients experiencing their first virological failure.

2. Materials and methods

This was a retrospective analysis of patient data held in France. Data for all patients were stored in a specifically designed anonymous database that included virological, demographic and therapeutic parameters.

2.1. Study population

Data were included in the analysis from patients who underwent successful ARV therapy and achieved plasma HIV RNA concentrations <50 copies/mL for ≥6 months before experiencing their first virological failure. Virological failure was defined as at least two consecutive measurements of plasma HIV RNA ≥50 copies/mL. Most patients (ca. 90%) underwent baseline genotypic assessment. For inclusion in the analysis, patients had to be receiving one of the following treatment regimens: N(t)RTIs + r/PI; N(t)RTIs + NNRTI; N(t)RTIs + INI; r/PI + NNRTI; r/PI + INI; or INI + NNRTI. Patients receiving any other regimen were excluded from the analysis. All patients were still under therapy at the time of genotypic resistance testing, meaning that the virus was still under the drug selection pressure and that resistance mutations could be detected if they existed.

2.2. Sample collection and HIV-1 sequence analysis

Patients provided blood samples on the occasion of their confirmed first virological failure. Plasma HIV-1 RNA was measured with a COBAS® AmpliPrep®/*Taq*Man® HIV-1 Assay v.2.0 (Roche Diagnostics, Basel, Switzerland). The second sample of detectable plasma HIV-1 RNA ≥50 copies/mL was used for performing genotypic testing. Reverse transcriptase, protease and integrase resistance genotypic analyses were conducted according to the Agence Nationale de Recherches sur le SIDA (ANRS) consensus method [6]. 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. Resistance was interpreted according to the last version of the ANRS algorithm (http://www.hivfrenchresistance.org).

2.3. Plasma HIV-1 RNA concentrations and 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.

2.4. Statistical analysis

Characteristics of the patients were described using either frequency for categorical variables or median [interquartile range (IQR)] for continuous variables. Fisher's exact test and Wilcoxon rank test were used to compare baseline characteristics of patients for categorical and continuous variables, respectively, with a level of significance at $P < 0.05$. Fisher's exact test was used to compare the percentage of patients with resistance mutations between the treatment groups.

3. Results

3.1. Patient disposition and treatment-related characteristics

Among 434 patients analysed who had experienced virological failure, resistance testing results were available in 416 cases (95.9%). Overall, the median level of plasma HIV-1 RNA at failure was 2.87 $\log_{10}$ copies/mL (IQR 2.29–3.84 $\log_{10}$ copies/mL). Among these 416 patients, 146 were receiving N(t)RTIs + r/PI, 152 were receiving N(t)RTIs + NNRTI, 37 were receiving N(t)RTIs + INI, 53 were receiving r/PI + NNRTI, 22 were receiving r/PI + INI and 6 were receiving INI + NNRTI. This study focused on patients receiving ritonavir-boosted darunavir, lopinavir or atazanavir as the PI component of their treatment regimen. This was because these PIs were the most widely prescribed at the time of the study design and also because the number of patients taking other PIs in the database did not allow meaningful analysis. The NNRTIs used were efavirenz in NRTI-based regimens and etravirine in regimens without NRTIs. The INI used in all cases was raltegravir. The N(t)RTIs used in the regimens were tenofovir, abacavir, emtricitabine and lamivudine. There were no statistically significant differences between the patients groups receiving or not receiving N(t)RTIs in terms of their demographic or clinical characteristics (Table 1).

3.2. Genotypic analysis

Overall, higher rates of drug resistance (number of patients with resistance to at least one ARV at failure) were observed in patients receiving N(t)RTI-sparing regimens compared with N(t)RTI-containing regimens ($P < 0.0001$) (Table 2). Some drugs had very different resistance profiles with regard to their condition of use. When the combination of N(t)RTIs + r/PI was used, PIs protect themselves and also the associated N(t)RTIs from the selection of resistance [resistance to PIs 0.7% and to N(t)RTIs 8.9%]; however, when the NNRTI + r/PI combination was used this

Table 1
Demographics and clinical characteristics in patients receiving N(t)RTI-based or N(t)RTI-sparing regimens ($N = 416$).

	N(t)RTI-based regimen ($n = 335$)	N(t)RTI-sparing regimen ($n = 81$)	*P*-value
Age (years) [median (IQR)]	41 (36–53)	40 (39–48)	≥0.05
Sex male [*n* (%)]	246 (73.4)	60 (74.1)	≥0.05
CD4 cell count at baseline (cells/mm^3) [median (IQR)]	354 (210–470)	361 (190–505)	≥0.05
Plasma HIV-1 RNA at baseline ($\log_{10}$ copies/mL) [median (IQR)]	4.8 (3.7–5.6)	4.9 (3.5–5.1)	≥0.05
Duration of last treatment before virological failure (weeks) [median (IQR)]	47 (36–62)	42 (38–59)	≥0.05

N(t)RTI, nucleos(t)ide reverse transcriptase inhibitor; IQR, interquartile range.