Transmitted drug resistance to rilpivirine in newly diagnosed antiretroviral naive adults

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Abstract

We characterized transmitted drug resistance to rilpivirine and the predicted efficacy of first-line rilpivirine-containing regimens in antiretroviral-naive Spanish patients. International Antiviral Society-USA mutations were detected in 138 of 2781 patients (4.9%), E138A (3.4%) being the most prevalent. Using the Stanford Algorithm, 121 patients (4.4%) showed low-level or intermediate resistance. No differences in the predicted efficacy of first-line non-nucleoside reverse transcriptase inhibitor-based regimens were observed. As rilpivirine becomes more widely used in clinical practice, the evolution of its transmitted drug resistance will need to be monitored. In addition, the exact role of E138A singletons on rilpivirine activity as part of first-line regimens merits further evaluation.

Keywords: Naive adults, resistance mutations, rilpivirine, therapeutic barrier

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The International Antiviral Society-USA (IAS-USA) update of drug-resistance mutations in human immunodeficiency virus type 1 (HIV-1) [1] describes 16 mutations associated with resistance to rilpivirine: K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C and M230I/L. As most of the studies characterizing transmitted drug resistance across Europe and the USA have not looked for some of these rilpivirine-resistance-associated mutations (RAMs) (e.g. mutations at codons 138, 221 and 227) [2–5], little information on the prevalence of transmitted rilpivirine RAMs is available [6–8]. We have previously reported transmitted drug resistance over different periods in Spain [9–11], but none of these reports evaluated rilpivirine transmitted drug resistance. In addition to transmitted drug resistance, we have also characterized clinically relevant transmitted drug resistance. For rilpivirine, it may also be of interest to know how certain singletons (e.g E138A) impact drug activity, especially when rilpivirine is part of a fully active first-line regimen. Again, it may be of interest to use clinically relevant resistance to build a therapeutic barrier with first-line antiretroviral regimens containing rilpivirine, and to compare it with other regimens that are currently recommended for first-line therapy.

In this study, we have investigated rilpivirine RAMs in 2781 patients from Cohorte de la Red de Investigación en Sida [12,13], antiretroviral naive adults consulting for the first time in collaborating HIV units from the public healthcare services, and recruited during the period 2007–2011. To describe rilpivirine RAMs we have used the 2013 update of the IAS-USA drug-resistance mutation list [1]. To evaluate clinically relevant resistance to rilpivirine, and to other first-line antiretrovirals, we have used the latest update of the Stanford HIV Database Algorithm (v 7.0 2014 Feb 27) [14]. Any category different from susceptible or potential low-level resistance was considered clinically relevant. Predicted efficacy of first-line regimens was evaluated through their genotypic sensitivity score, which was built by scoring susceptible as 1, intermediate (low-level or intermediate resistance) as 0.5, and high-level resistance as 0. A fully active regimen was considered when a genotypic sensitivity score of 3 was present. The sample was described using proportion or median (interquartile range) for categorical and continuous variables, respectively; bivariate analysis was performed using chi-squared or Kruskall–Wallis test as appropriate. Resistance mutations scored by IAS-USA and Stanford HIV database were described using prevalence, and the corresponding confidence intervals were calculated with an analytically derived variance estimator. All the analyses were conducted using STATA software (V.11.1, Stata Corporation, College Station, TX, USA).

IAS-USA rilpivirine RAMs were detected in 138 patients, making a total prevalence of 4.9% (95% CI 4.1–5.8). E138A

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alone was the most frequent mutation, representing a total prevalence of 3.4% (95% CI 2.7–4.1), followed by E138K (0.4%, 95% CI 0.2–0.7), H221Y (0.4%, 95% CI 0.1–0.6), Y181C (0.3%, 95% CI 0.05–0.5), K101E (0.2%, 95% CI 0.025–0.4), Y188L (0.2%, 95% CI 0.06 0.4), K101P (0.1%, 95% CI 0.01–0.3), E138G (0.1%, 95% CI 0.02–0.3), Y181I (0.1%, 95% CI 0.01–0.3) and M230L (0.03%, 95% CI 0.001–0.2). These data are consistent with the limited information presented so far: a French survey [7] documents a 5% global prevalence for rilpivirine-associated mutations, Italian researchers have presented data on a 6% prevalence [15], and data from the ECHO & THRIVE studies have shown similar numbers [16,17]. As in our study, E138A accounted for more than half of the prevalence of rilpivirine-associated mutations. There is evidence of some impact on phenotypic resistance to rilpivirine of site-directed mutants with changes at codon rt138 [18,19], and a selection of this mutation by HLA-B*18-restricted cytotoxic T lymphocytes [20] has been reported. E138A is now considered to have an impact on rilpivirine resistance by the most recent updates of international algorithms [14,21], but there is little evidence on the potential impact of the E138A mutation alone on clinical response to first-line rilpivirine-containing regimens. Although currently available information suggests that first-line rilpivirine-containing regimens are not indicated in the presence of a baseline E138A singleton, in terms of cross-resistance among non-nucleoside reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitors (particularly 3TC-FTC), clinical studies addressing this issue are needed.

As most of the isolates with rilpivirine RAMs carry E138A singletons, we have studied clinically relevant transmitted drug resistance, by means of the Stanford HIV Database Algorithm. Fully resistant isolates were associated with Y188L (n = 5; 0.2%, 95% CI 0.06–0.4), Y181I and K101P (n = 2; 0.1%, 95% CI 0.01–0.3) as singletons, while another six patients showed the combination of several mutations (A98G+K101E+Y181C, K101E+Y181C+G190A, K101E+Y181C+G190S, L100I+M230L, Y188F+M230L, L100I+M230L (n = 1; 0.04%, 95% CI 0.001–0.2, respectively). Intermediate resistance was associated with singletons of E138A (n = 91; 3.3%, 95% CI 2.6–3.9), E138K (n = 12; 0.4%, 95% CI 0.2–0.7), L100V (n = 5; 0.2%, 95% CI 0.1–0.4), E138G (n = 4; 0.1%, 95% CI 0.04–0.4), Y181C (n = 2; 0.1%, 95% CI 0.01–0.3), L100I (n = 2; 0.1%, 95% CI 0.01–0.3) and K101E (n = 1; 0.04%, 95% CI 0.001–0.2), while only six patients with the combination of two or more mutations were scored as intermediate (E138A+V179D (n = 2; 0.1%, 95% CI 0.01–0.3), K101E+E138A (n = 2; 0.1%, 95% CI 0.01–0.3) and A98G+G190A plus Y181C+H221Y+F227L (n = 1; 0.04%, 95% CI 0.001–0.2)). Clinically relevant resistance to first-line drugs approved in Spain is shown in Table 1.

Evaluating the predicted efficacy of a first-line regimen may be of importance for updating treatment guidelines and establishing recommendations on how resistance testing should be performed on newly diagnosed patients. In our study, rilpivirine-based first-line regimens showed non-significant differences in clinically relevant transmitted drug resistance (188 and 189 patients (6.8%, 95% CI 5.8–7.7) showed any relevant predicted resistance to any component of TDF+3TC/FTC+RPV and ABC+3TC/FTC+RPV, respectively) compared with efavirenz-based or nevirapine-based regimens (5.8–5.9% and 6.3%, respectively). On the other hand, regimens based on first-line protease inhibitors showed lower rates of predicted resistance, compared with rilpivirine-based regimens (Table 2). Evolution of transmitted drug resistance to rilpivirine will also need to be monitored over the following years, as this drug becomes more widely used in clinical practice.

Our study has several limitations. First, we have studied patients included in Cohorte de la Red de Investigación en Sida, a Spanish cohort of antiretroviral-naive adults. Although our results need to be reproduced in other cohorts, our findings of the prevalence of IAS-USA mutations are similar to those recently reported in France and Italy. Second, our sequencing data have been obtained through population sequencing and we

TABLE 1. Clinically relevant resistance to rilpivirine, and other first-line drugs, in antiretroviral naive Spanish adults through the period 2007–2011

ARV class	ARV drug	Intermediate	Prevalence (95% CI)	Resistant	Prevalence	p
NRTIs	Tenofovir	2	0.1 (0.01–0.3)	49	1.8 (1.3–2.3)	nd
	Emtricitabine	8	0.3 (0.1–0.5)	13	0.5 (0.2–0.7)	nd
	Lamivudine	8	0.3 (0.1–0.5)	13	0.5 (0.2–0.7)	nd
	Abacavir	61	2.2 (1.6–2.8)	4	0.1 (0.04–0.4)	nd
NNRTIs	Efavirenz	33	1.2 (0.8–1.6)	82	2.9 (2.3–3.6)	<0.0001
	Nevirapine	30	1.1 (0.7–1.5)	98	3.5 (2.8–4.2)	<0.0001
	Rilpivirine	123	4.4 (3.6–5.2)	14	0.5 (0.2–0.8)	reference
PIs	Lopinavir	7	0.2 (0.05–0.5)	1	0.04 (0.001–0.2)	<0.0001
	Atazanavir	19	0.7 (0.4–1.01)	2	0.1 (0.01–0.3)	<0.0001
	Darunavir	3	0.1 (0.02–0.3)	1	0.04 (0.001–0.2)	<0.0001

p values using rilpivirine as reference. Intermediate resistance was more frequently detected for rilpivirine than for efavirenz and nevirapine; conversely, fully resistant isolates were more frequently detected for efavirenz and nevirapine. For protease inhibitors, all comparisons were significant. As NRTIs are the backbone of first-line regimens, no comparison was made (nd). Abbreviations: ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.