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Rilpivirine resistance associated mutations in HIV-1 infected pregnant women☆

Mutaciones asociadas a resistencia a rilpivirina en embarazadas infectadas por VIH-1

Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens are a standard first-line antiretroviral therapy (ART) in Latin-American countries.[1] Despite its proven efficacy, the clinical use of first-generation NNRTIs, has been limited by their low genetic barrier and cross-resistance. Rilpivirine (RPV), a new second generation NNRTI, displays in vitro activity extending over other NNRTI-resistant HIV strains.[2–4] This drug has a US FDA use in pregnancy rating of category B and it is not recommended the use in pregnancy unless the expected benefit outweighs any potential risks,[5] and its final role in pregnancy remains to be determined. To date, there is no information about the rate of RPV resistance-associated mutations (RPV RAMs) in HIV-infected pregnant women (HPW). We aimed to evaluate the prevalence of RPV RAMs in ART-naive and experienced HPW and its impact in the susceptibility profile. During the period March 2008 to August 2012, baseline plasma VL samples from 112 HPW were analyzed. The prevalence of individual RPV RAMs K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C, M230I/L, Y188L and L100I + K103N combination, was investigated in these samples.[6] In patients with, at least, one RPV RAM (including polymorphic mutations, as E138A) the predicted susceptibility was inferred using the Stanford University Drug Resistance Database algorithm (version 7.0). Of 112 HPW, 46.4% ($n = 52$) were ART-naive and 53.6% ($n = 60$, of whom 11 had HIV acquired perinatally) were ART-experienced (all with baseline detectable viral load). The median (interquartile range, IQR) for age, gestational age, VL and CD4 T-cell counts were: 27 years (21–32); 20 weeks (12–26); 9188 copies/mL (2827–28,136) and 286 μL (197–508), respectively. The predominant HIV-1 subtype was B/F, which was found in 71.2%, followed by B/B (24%). In the experienced group, 65% ($n = 39$) had exposure to first generation

Table 1
Rilpivirine resistance associated mutations (RPV RAMs) and predicted susceptibility in HIV-infected pregnant women.

Patient #	Antiretroviral therapy status	Mode of transmission	Prior NNRTI exposure	RPV RAMs	RPV predicted susceptibility
1	Naive	Sexual	N/A	E138A	Low level resistance
2	Naive	Sexual	N/A	E138A	Low level resistance
3	Naive	Sexual	N/A	E138G	Low level resistance
4	Naive	Sexual	N/A	E138K	Intermediate resistance
5	Naive	Sexual	N/A	Y181I	High level resistance
6	Experienced	Sexual	EFV	Y181C	Intermediate resistance
7	Experienced	Perinatal	EFV	K101P	High level resistance
8	Experienced	Perinatal	EFV, NVP	Y181C, E138Q, H221Y	High level resistance
9	Experienced	Perinatal	NVP	H221Y, Y188L	High level resistance
10	Experienced	Perinatal	NVP, EFV	E138K, L100I + K103N combination	High level resistance
11	Experienced	Perinatal	EFV	Y188L	High level resistance
12	Experienced	Sexual	EFV	E138A	Low level resistance
13	Experienced	Perinatal	EFV	L100I + K103N combination	High level resistance
14	Experienced	Perinatal	EFV	E138K	Intermediate resistance
15	Experienced	Perinatal	EFV	Y181C	Intermediate resistance
16	Experienced	Sexual	None	E138A	Low level resistance

NNRTI: nonnucleoside reverse transcriptase inhibitor; EFV: efavirenz; NVP: nevirapine; N/A: not applicable.

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NNRTIs (23 to nevirapine, 11 to efavirenz, and 5 to both). None had prior or ongoing exposure to RPV or etravirine (ETR). Evidence of RPV resistance (%, IC95%) was found in 16/112 (14.3%, ±6.4) patients: 5/52 (9.6%, ±8) in naive and 11/60 (18.3%, ±9.7) in experienced HPW. Ten individual RPV RAMs were identified, with an overall prevalence of 4.5% (±3.8) for E138A; 3.6% (±3.4) for E138K; 2.7% (±3) for Y181C; 1.8% (±2.4) for Y188L and H221Y; 0.9% (±1.7) for E138G, E138Q, K101P, V179L and Y181I. The combination L100I + K103N was found in 2/60 (3.3%, ±4.5) experienced HPW, in one case associated with E138K mutation. Prior NNRTI (either efavirenz or nevirapine) use was observed in 91% experienced patients harboring RPV RAMs, with a median (IQR) exposure of 24 (6–115) months. No association with any subtype was found. Individual RPV RAMs profile, ART exposure and predicted RPV susceptibility are shown in Table 1. All naive pregnant women with RPV RAMs had evidence of, at least, reduced susceptibility to RPV while 9/11 (82%) experienced HPW had predicted intermediate or high level resistance. Despite the limited period of time and number of patients, some aspects should be highlighted. In a population of experienced HPW, 18.3% of patients had RPV resistance considering either individual RPV RAMs, L100I + K103N combination or both, which can be mostly attributed to prior exposure to first generation NNRTIs. In this context, a reduction in the susceptibility to the drug was observed in the majority of experienced patients harboring RPV RAMs. Anta et al. recently described that 19.3% genotypes from patients failing NNRTIs are RPV-resistant.[7] Considering exclusively NNRTI-experienced HPW in our cohort, 25% should be considered RPV-resistant (data not shown). Of note, none of our patients had exposure to ETR, which shares RPV's resistance profile.[4–8] However, the highest burden of RPV resistance was in women infected perinatally (8 of 11 patients) and had been heavily exposed to NNRTI-based ART, with irregular adherence. In this clinical scenery, cross RPV resistance could emerge as a result of long term non-adherence to first generation NNRTIs. Considering the naive patients, these preliminary data show a moderate prevalence of RPV RAMs. Reports of RPV RAMs in naive patients are limited.[9] Chueca et al. described an overall 7.7% RPV RAMS in HIV-1 infected patients, being E138A present in 5.5%.[10] Such prevalences are lower than those described here. The prevalence of RPV RAMs in naive HPW could be attributed, to cross resistance to first generation NNRTI-selected and, subsequently, transmitted drug-related mutations. As E138A polymorphism is one of the most prevalent RPV RAMs, development of a validated score could be clinically useful. Further research is needed to evaluate if HIV subtype has an influence in RPV resistance. Our study supports routine genotype before prescribing RPV in this population.

Conflict of interest

All authors declare no competing interests.

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Mucocutaneous leishmaniasis caused by *Leishmania infantum var Lombardi* in an immunocompetent patient, Spain

Leishmaniasis mucocutánea causada por Leishmania infantum var Lombardi *en un paciente inmunocompetente, España*

To the editor,

The initial lesion in mucocutaneous leishmaniasis (MCL) develops in a similar way to that of cutaneous leishmaniasis (CL). Usually after the skin lesion has healed, the infection remains dormant for a variable period of time, from weeks to several years. Mucocutaneous involvement frequently starts on the anterior nasal septum mucosa and appears as a small-sized hyperaemic nodule that rapidly evolves to an ulcer. The nasal septum is invaded, perforated and destroyed if no early treatment is started.[1]

Nearly 3% of the patients diagnosed with CL caused by *Leishmania braziliensis* will concomitantly or subsequently develop mucosal disease.[2] In contrast, *L. infantum* is not classically associated with MCL. We herein report a case of MCL caused by *L. infantum var lombardi* in an immunocompetent patient from Spain.

The patient was a 43-year-old healthy man from Madrid – Spain, who was referred to our dermatology department because of a