Rilpivirine Drug Resistant Mutations in Experienced Patients in Mexico. Impact on Long-Acting ART.

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BACKGROUND

There is currently considerable excitement in the antiretroviral treatment (ART) field on the prospect of long-acting, including oral, injectable, and implantable formulations. Long-acting cabotegravir and rilpivirine (CAB/RPV-LA) is the first injectable combination approved to treat virologically suppressed adults without history of treatment failure and with no known resistance to either cabotegravir or rilpivirine. Despite confirmed virological failure (CVF) in these trials was rare, baseline rilpivirine drug resistance mutations (DRMs) is one of the known risk factors. Accumulation of nonnucleoside reverse transcriptase inhibitors (NNRTIs) DRMs is common in low-and-middle-income countries (LMICs). We investigated rilpivirine cross-resistance in experienced patients in Mexico, where Efavirenz (EFV) was the preferred initial ARV drug for more than 10 years.

METHODS

Genotypic sequence data from 2573 patients experiencing at least two treatment failures were included for our analysis. Pol sequences were submitted to Stanford HIVdb v9.6 to identify rilpivirine DRMs and subtyping. The following mutations were included as rilpivirine DRMs (Stanford HIVdb penalty score ≥10): A98G, V100IV, K101EPH, V106I, E138AGKQR, V179DEFL, Y181CFGISV, Y188FL, G190ACEQSTV, H221Y, F227C, and 230IL. Resistance profiles were categorized as susceptible, potential low-level resistance, low-level resistance, intermediate or high-level resistance.

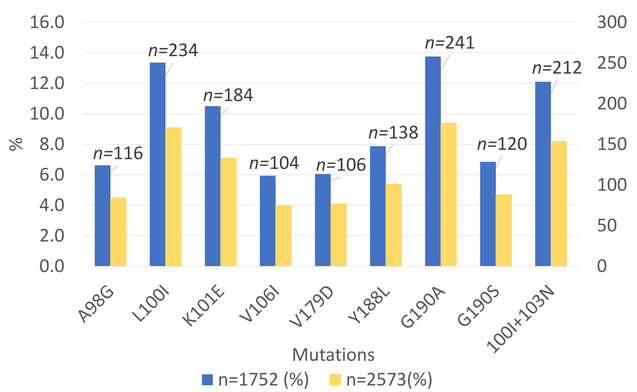


Figure 1. Prevalence of Rilpivirine DRMs in Experienced Mexican Patients

Our results indicate that in a setting where NNRTI-based treatment was the main initial ART for more than a decade, **rilpivirine DRMs are common in patients with at least 2 ART failures**. Our results have significant implications for the implementation of CAB/ RPV-LA, as screening for existing DRMs is logistically challenging in LMICs and could be a **barrier to use of CAB/RPV-LA**.

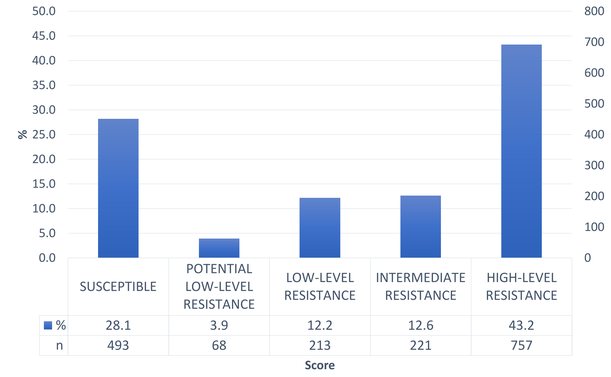


Figure 2. Rilpivirine Resistance profiles according to Stanford HIVdb in 1752 Experienced Mexican Patients

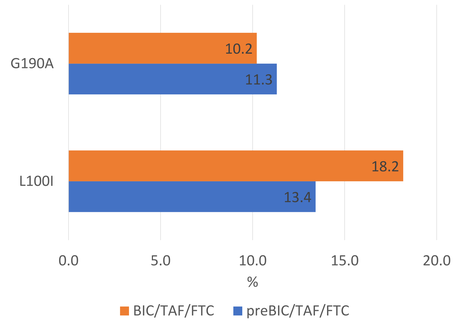


Figure 3. Frequency of L100I and G190A Pre and during BIC/TAF/FTC as Initial ART in Mexican Patients

RESULTS

Patients failing two or more ART combinations (n=2573) were included, all belonging to subtype B virus. All our cases had previous treatment failure to NNRTIs, mostly to EFV. Of those, 1752 (68%) presented with at least one NNRTI DRM, including 675 (26.2%) with at least one rilpivirine DRM and 377 (14.6%) with at least two rilpivirine DRMs. Rilpivirine DRMs or combinations with more than 4% frequency are presented in Figure 1,in yellow with relation to the total sample and in blue related to those with DRMs. DRMs, L100I, K101E, Y188L and G190A were the most frequent found with more than 5% prevalence, as well as the combination of L100I and K103N related to EFV failure.

More than three quarters of cases with rilpivirine DRMs, showed low level resistance (12.2%; n=213); intermediate (12.6%; n=221) and high-level rilpivirine resistance (43.2%; n=757), Figure 2. Frequency of the most common rilpivirine DRMs did not change markedly between the era of EFV preferred initial therapy (preBIC/TAF/FTC) and the years on integrase preferred ART (since 2019), Figure 3.

CONCLUSIONS

This retrospective analysis indicates that rilpivirine DRMs are common in a setting wherein NNRTI-based treatment was widely implemented, and has implications for operational implementation of CAB/RPV-LA. While the prevalence of NNRTI pretreatment resistance will likely decrease over time with the widespread use of integrase inhibitors, which started in 2019 in Mexico, the persistence of NNRTI mutations in the large number of patients who have been exposed to NNRTI-based treatment in the past, makes possible that transmission of NNRTI-resistant virus will continue for some time, and could impact with mutants with high level resistance to Rilpivirine (43%). Transmitted resistance of rilpivirne DRMs was not frequent in the previous surveys performed in México, but is more frequent in other cohorts like the Italian ARCA, Figure 4. We acknowledge that our resistance data was not obtained from patients with a suppressed viral load, and that most of them are not using NNRTIs in the current ART when the genotypic test was performed, so the prevalence of rilpivirine DRMs might be underscore

Unfortunately, screening for existing rilpivirine DRMs is logistically and technically challenging in Mexico as in other LMICs, and could be a barrier for the use of CAB/RPV-LA.

	NNRTI SECONDARY DRMs	TRANSMITTED DRUG RESISTANCE		
	MEXICO (n=1752)	TDR MEXICO (Avila, 2016)	TDR SPAIN (GESIDA 2023)	TDR ITALY (ARCA 2023)
L100I	13.4%	0.5%	0.1%	3.2%
K101E	10.5%	0.8%	0.8%	6.7%
Y188L	7.9%	0.5%	0.3%	0.7%
G190A	13.8%	0.8%	0.7%	9.2%
K103N	49.3%	4.2%	4.9%	17.6%

Figure 4. Frequency of Rilpivirine DRMs in TDR surveys from Mexico and Europe.

ADDITIONAL KEY INFORMATION

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