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Rilpivirine Resistance-associated Mutations among Antiretroviral-naive Patients Infected with HIV-1 in Asia

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To the Editors

HIV-1 infection in Asia accounts for a major proportion of the global HIV-1 epidemic.[1] After rapid scale-up of combination antiretroviral therapy (ART), HIV-associated mortality and morbidity in this region have been significantly reduced.[2–6] Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens are used in the majority of patients on first-line ART in Asia, particularly in developing countries.[7] Rilpivirine (RPV), a new NNRTI of the diarylpyrimidine family, was recently approved by the US Food and Drug Administration (FDA) to be used in ART-naïve patients, [8] based on its safety and sustained efficacy.[9,10] RPV-based regimens would thus be a valid alternative to first-generation NNRTI-based regimens in Asia, particularly in patients who cannot tolerate both nevirapine (NVP) and efavirenz (EFV). A previous study demonstrated the significant (6.5%) prevalence of resistance-associated mutations (RAMs) to NVP, EFV, or etravirine (ETR) among treatment-naïve patients, raising the concern of primary drug resistance to NNRTIs in Asia.[11] However, primary drug resistance to RPV in this region has never been evaluated. It has been well established that primary drug resistance can threaten the effectiveness of ART among HIV-1–infected patients who are initiating ART.[12]

Fifteen reverse transcriptase mutations (K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C, and M230I/L) associated with decreased susceptibility to RPV have been described in the International Antiviral Society–USA (IAS–USA) drug resistance mutations list.[13] TREAT Asia (Therapeutics, Research, Education and AIDS Training in Asia) is a network of clinics, hospitals and research institutions working to ensure safe and effective delivery of HIV/AIDS treatment throughout the Asia-Pacific. This network has developed the TREAT Asia Studies to Evaluate Resistance (TASER) in order to monitor HIV-1 drug resistance in Asia.[14] The majority of patients enrolled in TASER studies are infected with HIV-1 non-B subtypes, mostly CRF01_AE.[14] It is therefore relevant to study RPV RAMs among ART-naive patients infected with HIV-1 non-B subtypes in this cohort.

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The primary objective of this study was to determine the prevalence of RPV RAMs among this group of ART-naïve HIV-1-infected patients, in order to estimate the potential use of RPV as a first-line NNRTI in Asia. Secondary objectives were to compare the prevalence of RPV RAMs between patients infected with HIV-1 non-B and B subtypes, and to determine other clinical factors that are associated with the presence of RPV RAMs.

ART-naïve patients with available pre-treatment reverse transcriptase genotypes from the TASER-Monitoring Study (TASER-M) cohort were selected for inclusion in the study. TASER-M recruitment began in 2007, with a total of 11 participating sites from Thailand, Hong Kong, Malaysia, the Philippines and Indonesia. Ethics approvals were obtained from the institutional review boards at the participating clinical sites, and coordinating and data management centers. Informed consent was obtained from participants prior to enrolment.

FASTA files were interpreted using the Stanford University HIV Drug Resistance Database tools (Stanford HIVdb, version 6.1.1) for genotyping and REGA HIV-1 Subtyping Tool - Version 2.0 for subtyping. Mutations were analyzed using the IAS-USA 2011 mutation list. Fifteen reverse transcriptase mutations (K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C, and M230I/L) associated with decreased susceptibility to RPV.

Comparison of categorical data was performed using chi squared or fisher's exact test, while the Wilcoxon rank sum test was used to compare continuous data. Baseline factors associated with the presence of at least one or more RPV RAMs were analyzed using a logistic regression model. We defined the baseline as the time period up to six months prior to starting ART. If multiple FASTA files, CD4 and HIV RNA measurements were available during the baseline period, only those closest to start of ART were chosen for analysis. In the logistic model, factors with significant univariate p-values at the 10% level were chosen for inclusion in the multivariate model, using a forward stepwise method. Covariates were considered significant in the multivariate model if p-values were <0.05. Site's income levels were grouped according to World Bank classifications (22 June 2012).[15] The statistical analyses were performed using SAS (Version 9.2, SAS Institute Inc., Cary, NC) and STATA (Version 12.1, StataCorp, College Station, TX).

A total of 1,627 HIV treatment-naïve patients were analyzed. The median age was 36 (IQR 30 – 44) years, with 68% of the patients being male. The predominant mode of exposure was heterosexual contact (68%), and the median pre-treatment CD4 and HIV RNA were 107 cells/μL and 100,000 copies/ml, respectively. The main subtypes were of non-B types (83%), with CRF01_AE representing 74% of the overall subtypes.

Overall, 48 (3.0%) had at least one or more RPV RAMs. The RPV RAMs based on the IAS-USA 2011 list were K101E (0.1%), K101P (0.1%), E138A (1.0%), E138G (0.7%), E138K (0.1%), V179L (0.1%), Y181C (0.7%), H221Y (0.2%), F227C (0.1%) and M230I (0.1%); 10 of 15 RPV RAMs were identified.

Baseline characteristics including age, gender, mode of exposure, country income level, CD4 and HIV RNA measurements, previous AIDS diagnosis and HIV-1 subtype were included in the univariate logistic regression model to determine if these factors were significantly associated with the presence of at least one or more RPV RAMs prior to starting ART (Table 1). The univariate model indicates that the only factor associated with the presence of RPV RAMs was country income level. Patients residing in countries classified as "Lower Middle" income were more than twice as likely to harbor RPV RAMs than those who were from "Upper Middle" or "High" income countries [odds ratio (OR) = 2.41, 95% confidence interval (CI): 1.10 to 5.26, p-value = 0.027]. As no other factors were found to be significantly associated with RPV RAMs, the planned multivariate regression model was not attempted.

The presence of HIV-1 drug resistance mutations, particularly involving NNRTI resistance, among treatment-naïve patients is significantly associated with increased risk of virologic failure with first-line ART.[16] This study demonstrates a prevalence of primary drug resistance to RPV among ART-naïve patients in this cohort in Asia of 3%. The most common RPV RAMs were E138A, E138G, and Y181C. However, E138K, a RPV RAM which is associated with greatest reduction in RPV susceptibility,[17,18] was observed in only 0.1% of patients. Although there is a concern that HIV-1 non-B subtype polymorphisms may reduce susceptibility to RPV, the results from the present study did not show any differences of RPV RAMs between HIV-1 B and non-B subtypes. Thus, based on these results and the low level of genotyped drug resistance, RPV would be expected to be a reliable alternative NNRTI for first-line ART in ART-naïve patients in Asia. Differences in human resources, access to medicines, healthcare infrastructure and capacity, and public health management between countries of varying income levels may contribute to the emergence of primary HIV drug resistance – which is not limited to only RPV. The fact that the lower-middle income countries were more likely to use NNRTI almost exclusively in the first-line regimens, as opposed to the higher income settings where PIs are used in first-line, may result in the higher prevalence of primary drug resistance of NNRTI including RPV.

In summary, we observed a low prevalence of RPV RAMs among ART-naïve patients infected with HIV-1 of both B and non-B subtypes in Asia. Patients from lower middle-income countries had higher levels of RPV RAMs, potentially reflecting the broader use of NNRTIs in first-line ART regimens. RPV could be an alternative NNRTI for first-line ART, particularly in patients who cannot tolerate both NVP and EFV.

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Table 1

Univariate analysis of factors associated with the presence of RPV RAMs

Factors	OR	95%CI	p-value*	Global p-value**
Age, years				0.767
18–30	1			
31–40	0.76	0.37 to 1.56	0.457	
41–50	0.99	0.46 to 2.14	0.985	
>50	0.72	0.23 to 2.21	0.564	
Sex				0.821
Male	1			
Female	1.07	0.58 to 1.97	0.821	
Exposure				0.177
Heterosexual contact	1			
Homosexual contact	0.93	0.44 to 1.98	0.847	
Other/Unknown	1.98	0.92 to 4.25	0.079	
Country income level				0.027
Upper middle + High	1			
Lower middle	2.41	1.10 to 5.26	0.027	
Previous AIDS				0.721
No	1			
Yes	0.89	0.49 to 1.65	0.721	
CD4, cells/μl				0.156
≤50	1			
51–100	0.65	0.26 to 1.65	0.369	
101–200	0.6	0.27 to 1.34	0.217	
>200	0.61	0.28 to 1.31	0.203	
HIV RNA, copies/ml				0.931
≤50,000	1			
50,001–250,000	0.98	0.50 to 1.93	0.950	
>250,000	0.97	0.44 to 2.11	0.931	
HIV-1 subtype				0.928
B	1			
Non B	1.04	0.48 to 2.24	0.928	

*Individual p-values are adjusted for missing values.

**Global p-values for age, CD4 and HIV RNA are tests for trend. Global p-values exclude missing values.