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High Prevalence of Genotypic Resistance to Integrase Inhibitors of HIV-1 Strains from ARV-Naïve Patients in Taiwan

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Background: Integrase inhibitor (II) in combination with 2 nucleoside reverse-transcriptase inhibitors is an effective treatment option for antiretroviral (ARV)-naive HIV-1-infected patients. In Taiwan, raltegravir was first introduced in 2009 as a second-line ARV and a pilot study by our laboratory in 2011 revealed that no HIV-1 strains harbored II-related major genetic mutations among the 160 analyzed specimens from ARV-naive patients. In this study, we aimed to determine the prevalence of II-related genetic mutations after the implementation of regulations on the prescription of HAART to ARV-naive patients by the Taiwan Centers of Disease Control (CDC) on 1 June 2012, by which raltegravir can only be used in combination with zidovudine/lamivudine in ARV-naive patients or with other ARVs in ARV-experienced patients.

Methods: Genotypic resistance assays were performed in the HIV strains from ARV-naïve patients (N=810) and ARV-experienced patients who were never exposed to II (N=198) at the designated hospitals around Taiwan from June 2012 to December 2014. Resistance mutations to II were identified using the HIVdb program of the Stanford University HIV Drug Resistance Database. Phylogenetic tree was constructed to determine the relationship among the resistant strains identified.

Results: Of the 1008 HIV-1 strains from patients never exposed to II, the majority were subtype B (85.5%), followed by CRF07_BC (9.5%), and CRF01_AE (4.8%). The overall prevalence of transmitted drug resistance (TDR) to II was 4.0% (n=40), which includes 35 HIV-1 strains of subtype B, 3 CRF07_BC, and 2 CRF01_AE. The prevalence of TDR to II increased from 2.9% in the third quarter of 2012, peaked at 8.8% in the first quarter of 2013, and gradually declined to 2.7% in the last quarter of 2013 **(Figure 1).** Among the identified II-related genetic mutations, Q148H/K/R and N155H/S/T were found in 22.5% (N=9) and 30% (N=12) of the II-resistant strains, respectively. The increased prevalence to II coincided with the increased percentage of Q148H/K/R and N155H/S/T mutations detected. Other mutations identified include E92Q/K/V (N=4), T97A (2), E138K (1), Y143R (1), Q146P (1), S147G(1), V151AL(1), E157Q (7), R263K (4), S230R(1), and R263K(3).

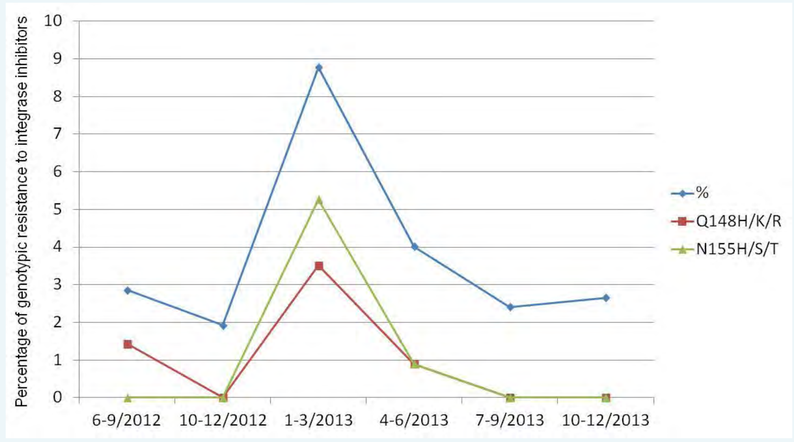

Figure 1. Trend of genotypic resistance to integrase inhibitors. Blue, percentage of genotypic resistance to integrase inhibitors; Red, percentages of Q148H/K/R variants; Green, percentages of N155H/S/T variants.

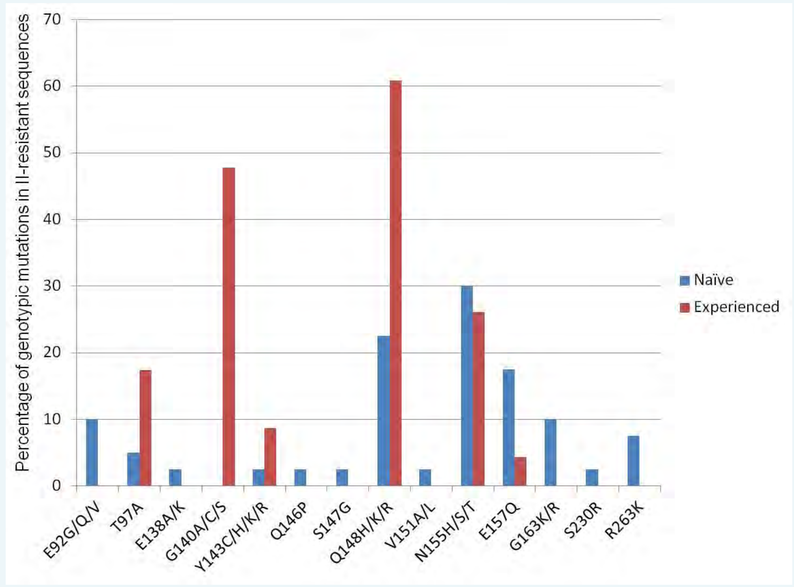

Figure 2. Percentages of genotypic mutations in integrase inhibitors (II)-resistant sequences amplified from II-naïve (blue bar) and II-experienced patients (red bar).

The genetic mutations related to II resistance were also analyzed in strains from II-experienced patients (N=107), which were compared with those from II-naïve patients (Figure 2). The distributions of genotypic mutations related to II resistance were different between the strains from II-naïve and those from II-experienced patients. For example, no G140S mutation was detected in strains from II-naïve patients which was predictive of resistance to II. Phylogenetic analysis showed that there was no clustering observed among these II-resistant sequences **(Figure 3)**.

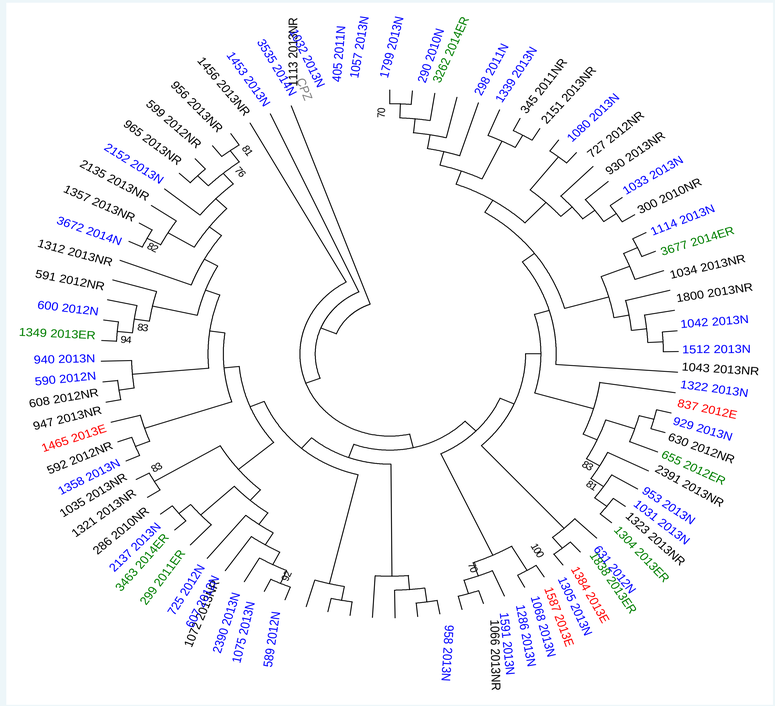

Figure 3. Phylogenetic tree analysis of integrase sequences from HIV-1-infected patients. Black, ARV-naïve and resistant to II; Blue, ARV-naïve and susceptible to II; Green, ARV-experienced and resistant to II; Red, ARV- experienced and susceptible to II.

Conclusions: In Taiwan, the prevalence of transmitted drug resistance to integrase inhibitors recently increased to 4.0%, which was temporally related to the implementation of regulations on the use of ARV drugs in ARV-naïve patients..