HIV-1 Drug Resistance Mutations Among Antiretroviral-Naïve HIV-1–Infected Patients in Asia: Results From the TREAT Asia Studies to Evaluate Resistance-Monitoring Study

Sommuek Sungkanuparph,1 Rebecca Oyomopito,6 Sunee Sirivichayakul,2 Thira Sirisanthana,4 Patrick C. K. Li,7 Pacharee Kantipong,5 Christopher K. C. Lee,5 Adeeba Kamarulzaman,3 Liesl Messerschmidt,2 Matthew G. Law,5 and Praphan Phanuphak2 on behalf of the TREAT Asia Studies to Evaluate Resistance-Monitoring Study (TASER-M)9

1Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 2HIV-NAT/Thai Red Cross AIDS Research Centre and Faculty of Medicine, Chulalongkorn University, and 3Therapeutics, Research, Education and AIDS Training in Asia (TREAT Asia), The Foundation for AIDS Research, Bangkok, and 4Research Institute for Health Sciences, Chiang Mai, and 5Chiang Rai Regional Hospital, Chiang Rai, Thailand; 6National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia; 7Queen Elizabeth Hospital, Hong Kong, China; 8Hospital Sungai Buloh, Sungai Buloh, and 9University of Malaya, Kuala Lumpur, Malaysia

(See editorial commentary by Jordan on pages 1058–1060.)

Of 682 antiretroviral-naïve patients initiating antiretroviral therapy in a prospective, multicenter human immunodeficiency virus type 1 (HIV-1) drug resistance monitoring study involving 8 sites in Hong Kong, Malaysia, and Thailand, the prevalence of patients with ≥1 drug resistance mutation was 13.8%. Primary HIV drug resistance is emerging after rapid scaling-up of antiretroviral therapy use in Asia.

Human immunodeficiency virus type 1 (HIV-1) infection in Asia accounts for a substantial proportion of the global HIV-1 epidemic. Currently, an estimated 4.7 million HIV-1–infected persons are living in Asia [1]. Combination antiretroviral therapy (ART) has significantly reduced mortality and morbidity in the region [2–6]. ART use has been scaling up in Asia for 2–9 years, depending on the country and setting [1, 7]. HIV-1 drug resistance (HIVDR) is a major reason for treatment failure, and primary HIVDR threatens the effectiveness of ART among HIV-1–infected patients who are initiating ART [8–10]. Primary HIVDR is defined as an increase in resistance of HIV-1 to antiretroviral drugs that is seen in individuals who have never received ART and presumably have been infected with drug-resistant virus [11, 12]. The prevalence of primary HIVDR varies from 6.2% to 21% in the United States and Europe, which suggests an increasing trend across the region [8–10]. However, the data on primary HIVDR in Asia is markedly limited. Two small studies in Thailand have reported the prevalence of primary HIVDR as being <5% [13, 14]. There are few widely available antiretroviral regimens in Asia, especially in countries with limited resources, and hence the detection of baseline HIVDR is of great importance.

Therapeutics, Research, Education and AIDS Training in Asia (TREAT Asia) is a network of clinics, hospitals, and research institutions working to ensure the safe and effective delivery of treatments of HIV infection and AIDS in Asia. To assess the extent of HIVDR in Asia, the TREAT Asia Studies to Evaluate Resistance-Monitoring Study (TASER-M) was initiated [15]. The objectives of TASER-M are to assess the prevalence and incidence of emerging HIVDR and to produce evidence to inform future treatment guidelines. This analysis aims to determine the prevalence and risk factors of HIVDR among antiretroviral-naïve HIV-1–infected patients recruited to the TASER-M cohort.

METHODS

Patients eligible for TASER-M are those initiating first-line ART or switching to second-line ART [15]. Antiretroviral-naïve patients who initiated ART at participating sites from April 2007 through March 2009 were included in this analysis. Patients with a history of monotherapy or dual therapy or exposure to antiretroviral drugs for prevention of mother-to-child transmission were excluded. Ethics approvals were obtained from local institutional review boards. Informed consent was obtained prior to genotypic resistance testing.

Genotype tests were performed locally with externally quality-controlled in-house and commercial assays on samples collected within 6 months prior to initiating ART. HIV-1

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drug-resistance–associated mutations (RAMs) were assessed using International AIDS Society–USA 2009 criteria [16]. Subtype was determined on the basis of genotypes of reverse transcriptase and protease genes. Laboratories providing genotyping results for the TASER-M study were required to participate in the TREAT Asia Quality Assurance Scheme, which is an assessment program to build genotyping laboratory capacity [17].

Data were collected on age, sex, ethnicity, HIV-1 exposure category, Centers for Disease Control and Prevention (CDC) disease stage classification, hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection status, CD4+ cell count, HIV-1 RNA level, and HIV-1 subtype. The prevalence of primary HIVDR was determined. Predictors of HIVDR were assessed using logistic regression models. A P value of <.05 was considered to be statistically significant.

RESULTS

A total of 682 patients from 8 sites including Hong Kong (2 sites), Malaysia (2 sites), and Thailand (4 sites) were included in this analysis. The mean age was 38.2 years (SD, 10.1 years); 65.5% of the patients were male. The ethnicities of patients included Thai (500, 73.3%), Chinese (134, 19.6%), Malay (26, 3.8%), Indian (7, 1.0%), Indonesian (3, .4%), Filipino (1, .1%), and others (11, 1.6%). The majority (74.9%) of patients reported heterosexual contact as their primary risk exposure for HIV-1; other risk categories included homosexual contact (18.2%), intravenous drug use (2.3%), receipt of blood products (.3%), and mixed exposure (3.2%). More than one-third of patients were in CDC disease stage C. The median CD4+ cell count was 100 cells/μL (interquartile range, 34–201 cells/μL), and the median HIV-1 RNA level was 100,000 copies/mL (interquartile range, 43,581–6,040,000 copies/mL). Overall, 77.7% of patients were infected with HIV-1 subtype CRF01_AE; other subtypes included B (16.3%), C (.7%), A (.1%), other Circulating Recombinant Forms (CRFs) (2.4%), or were missing (2.9%). Co-infection with HBV was seen in 5.1% of patients, and that with HCV was seen in 7.9% of patients.

The prevalence of patients with >1 RAM to any drug class was 13.8%, including RAMs to nucleoside reverse transcriptase inhibitors (NRTIs; prevalence, 8.4%), nonnucleoside reverse transcriptase inhibitors (NNRTIs; prevalence, 6.5%), and protease inhibitors (PIs; prevalence, 4%). Figure 1 shows the distribution and frequency of each RAM that was detected. K70R was the most common RAM to NRTIs (52 patients [7.6%]); M41L, D67N, T69S, M184V, L210W, T215Y, and K219Q were observed in <1% of patients. RAMs to etravirine were detected in 44 patients (6.5%) and those to efavirenz or nevirapine in 4 patients (.6%). The most common RAMs to etravirine were V179D (22 patients [3.2%]) and V106I (13 patients [1.9%]); other RAMs were found in <1% of patients. The RAMs observed to efavirenz or nevirapine were Y181C (3 patients [.4%]), V108I (1 patient [.1%]), and G190A (1 patient [.1%]). RAMs D30N, M46I, and I54M to PIs were each observed in .1% of patients (1 patient each).

The median CD4+ cell count was significantly lower among patients with RAMs when compared with those without RAMs (66 vs 108 cells/μL, respectively; P = .009). There were no differences between patients with RAMs and those without RAMs in age, sex, site location, ethnicity, risk exposure, HIV-1 subtype, HBV co-infection, HCV co-infection, or HIV-1 RNA level.

DISCUSSION

The emergence of primary HIVDR in antiretroviral-naïve patients has been associated with increased mortality, morbidity, and medical expenditures [8–10, 18, 19]. The longer history of ART availability in the participating sites in the region coupled with early suboptimal treatment regimens [20, 21] may be leading to the higher levels of circulating HIVDR mutations in the community. Because of the limited options available for second- or third-line ART, monitoring of HIVDR is a key to preparing for optimal treatment management in the future. The prevalence of primary HIVDR in the present study was higher than that found in previous surveys of transmitted HIVDR in this region [14, 22]. However, these 2 previous studies were conducted among newly infected patients, whereas the present study was performed among patients with chronic infection prior to ART initiation. The reported prevalence of

Figure 1. Distribution of resistance-associated mutations among 682 antiretroviral-naïve human immunodeficiency virus type 1 (HIV-1)–infected patients.
antiretroviral resistance among ART-naïve HIV-infected persons in Sub-Saharan Africa, where there are also resource-limited settings, ranged from 7.8% to 9.8% [23, 24].

Resistance mutations to NRTIs and NNRTIs were more commonly observed compared with those to PIs. The most common forms of primary or transmitted HIVDR that are detected globally are resistance mutations to NRTIs [18, 25–29]. In this study, the most common RAM was K70R, a thymidine analogue mutation, which is also consistent with the widespread use of zidovudine and stavudine [30, 31]. The use of zidovudine and stavudine in dual-therapy regimens also has contributed to the increased prevalence of this mutation [14, 32]. Previous studies have demonstrated that K70R was one of the most common RAMs observed among antiretroviral-naïve patients particularly in areas with early scaling-up of ART [33–37].

The low rate of M184V in the present study may be explained by the fact that the present study was conducted among patients with chronic infection prior to ART initiation. It is possible that our patients may have acquired drug-resistant HIV in the earlier period because dual therapy (ie, stavudine or zidovudine plus didanosine) was used in this region.

Interestingly, the prevalence of RAMs to etravage was higher than that of RAMs to efavirenz or nevirapine. This might be explained by the fact that the most common HIV-1 subtype in the present study was HIV-1 subtype CRF01_AE. A recent study has reported that non-B HIV-1 subtypes have natural polymorphisms that are described as RAMs to etravage [38]. Further study to evaluate the potential of these polymorphisms to affect etravage susceptibility is needed.

The pre-ART CD4+ cell counts of patients in this study were much lower than the set thresholds, with half of the patients having CD4+ cell counts of <100 cells/µL. In addition, the median CD4+ cell count was significantly lower among patients with RAMs compared with that among patients without RAMs. This finding supports the idea that patients with advanced HIV-1 disease might be at greater risk of having acquired drug-resistant HIV-1 infection earlier in the regional HIV epidemic, when regimens were not as potent.

In Asia, the new local guidelines and World Health Organization (WHO) guidelines recommend the use of nevirapine or efavirenz with lamivudine and zidovudine or tenofovir for first-line ART [39, 40]. According to our findings of a high prevalence of primary HIVDR, particularly RAMs to NRTIs, there is a risk of early treatment failure with the first-line ART in this region. Currently, guidelines in North America and Europe recommend resistance testing prior to initiation of ART [41, 42]. However, treatment guidelines for developing countries in Asia (eg, WHO and Thai guidelines) do not recommend this test in antiretroviral-naïve patients [41, 42], mainly because of the limited data on primary HIVDR in this region and the relatively high cost of the test. This raises concerns regarding the risk of treatment failure among patients with primary HIVDR. Further study to define a cost-effective strategy for detection of primary HIVDR in Asia is needed.

There are some limitations to the present study. First, the patients in the present study were tested for HIV-1 genotypes at pretreatment rather than at the time of diagnosis. Some resistance mutations may have reverted to the wild type. Thus, the prevalence of primary HIVDR could be underestimated. Second, the present study was conducted in a limited region of Asia, including 8 sites in only 3 countries, because of the limited availability of genotype tests in Asia.

In summary, primary HIVDR is emerging in Asia after rapid scale-up of ART use. Patients with a lower pre-ART CD4+ cell count were at higher risk for having primary HIVDR. Although HIV genotype testing prior to ART initiation is not routinely recommended in resource-limited settings, our results raise concerns about the risk of early treatment failure in our cohort if genotype testing is not conducted prior to initiation of ART.

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References

APPENDIX

Members of the TASER study. P. C. K. Li (steering committee member and protocol co-chair) and M. P. Lee, Queen Elizabeth Hospital, Hong Kong, China; K. H. Wong, Integrated Treatment Centre, Hong Kong, China; N. Kumarasamy (steering committee member and protocol chair) and S. Saghayam, YRG Centre for AIDS Research and Education, Chennai, India; S. Pujari (steering committee member) and K. Joshi, Institute of Infectious Diseases, Pune, India; T. P. Merati (steering committee member) and F. Yuliana, Faculty of Medicine, Udayana University and Sanglah Hospital, Bali, Indonesia; C. K. C. Lee (steering committee member) and L. L. Low, Hospital Sungai Buloh, Kuala Lumpur, Malaysia; A. Kamarulzaman (steering committee member Protocol co-chair) and L. Y. Ong, University of Malaya, Kuala Lumpur, Malaysia; M. Mustafa (steering committee member) and N. Nordin, Hospital Raja Perempuan Zainab II, Kota Bharu, Malaysia; R. Ditangco (steering committee chair) and R. O. Bantique, Research Institute for Tropical Medicine, Manila, Philippines; Y. M. A. Chen (steering committee member Protocol chair), Y. J. Chen, and Y. T. Lin, AIDS Prevention and Research Centre, National Yang-Ming University, Taipei, Taiwan; P. Phanuphak (steering committee member) and S. Sirivichayakul, HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; S. Sungkanuparp (steering committee member) and S. Kiertiburanakul, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; T. Sirisanthana (steering committee member) and J. Praparthananpan, Research Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand; P. Kantipong (steering committee co-chair) and P. Kambua, Chiang Rai Regional Hospital, Chiang Rai, Thailand; J. Y. Choi (steering committee member) and S. H. Han, Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea; W. Ratanaasuwan (steering committee member) and R. Sriondee, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; R. Kantor (steering committee member), Brown University, Rhode Island; A. H. Sohn, L. Meserschmidt (steering committee member), and T. Singtora (TREAT Asia, The Foundation for AIDS Research (amfAR), Bangkok, Thailand; and D. A. Cooper, M. G. Law (steering committee member), A. Jiamsakul, and J. Zhou, National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia.