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## Detection of human immunodeficiency virus type 1 transmitted drug resistance among treatment-naive individuals residing in Jakarta, Indonesia

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### Abstract

The presence of transmitted drug resistance (TDR) in human immunodeficiency virus type 1 (HIV-1) infected individuals naive to antiretroviral therapy, may affect the effectiveness of treatment. Jakarta, the capital city of Indonesia, recorded the highest number of cumulative HIV infection cases in the country. This study aimed to identify on the appearance of TDR, as well as to identify HIV-1 subtypes circulating among treatment-naive individuals in Jakarta. Whole blood samples collected from 43 HIV-1 infected, treatment-naive individuals. Viral subtyping and drug resistance testing were performed on HIV-1 *pol* genes amplified using nested polymerase chain reaction. CRF01\_AE was detected most frequently in Jakarta (73.08%). Drug resistance-related major mutation was not detected in protease fragments of *pol* gene, but two major mutations, K103N (6.67%) and Y181C (6.67%), were detected in reverse transcriptase fragments of *pol* gene. Our results suggest that TDR was emerged in Jakarta at a certain extent, thus further surveillance study to monitor the TDR prevalence and circulating HIV-1 subtypes in this region is considered to be necessary.

### Introduction

Indonesia reported increasing cases of human immunodeficiency virus (HIV) infections each year. The country recorded 280,623 cumulative cases of HIV infection in 2017, with 48,300 new cases among them.<sup>1</sup> Indonesia contributed to 18% of new HIV infection and 23% acquired immune deficiency syndrome (AIDS)-related deaths in Asia and the Pacific.<sup>2</sup> Jakarta, the capital city of Indonesia, has the highest number of cumulative HIV-infection cases in the country. The city recorded a total of 51,981 HIV cases, with 9,215 AIDS cases.<sup>1</sup>

As many other countries, HIV infection in Indonesia is mainly caused by HIV type 1 (HIV-1) group M. There are nine subtypes (B, C, D, F, G, H, J, and K), as well as circulating recombinant forms (CRFs) and unique recombinant forms (URFs), within the group M.<sup>3</sup> Several studies have reported the dominance of HIV-1 CRF01\_AE in several Indonesian regions.<sup>4-10</sup>

As an effort to address the HIV epidemic, Ministry of Health of Indonesia implemented antiretroviral therapy (ART) under national guideline. First-line ART regimen recommended contains two nucleoside reverse transcriptase (RT) inhibitors (NRTIs) and one non-nucleoside RT inhibitor (NNRTI). Zidovudine (AZT), lamivudine (3TC), tenofovir (TDF), and emtricitabine (FTC) are commonly used NRTI in Indonesia, while nevirapine (NVP) and efavirenz (EFV) are commonly used NNRTI. For HIV-1-infected individuals suffering treatment failure despite high adherence to ART, second-line regimen employing two NRTIs and one ritonavir-boosted protease (PR) inhibitor (PI) is recommended.<sup>11</sup>

ART strongly suppresses viral replication and maintain a healthy condition of infected individuals on ART; however, the presence of drug resistant viruses might compromise treatment success.<sup>12</sup> The emergence of acquired drug resistance (ADR) in treatment-experienced individuals and transmitted drug resistance (TDR) in treatment-naive individuals residing in several Indonesian regions, including Surabaya, Riau, Bali, and Maumere, has been previously described.<sup>5-10</sup> The TDR might disrupt effectiveness of treatment, resulting in unfavorable clinical outcomes.<sup>13</sup> Therefore, it is important to monitor the emergence of TDR by a continuous surveillance in order to secure long-term and stable ART in Indonesia.

The United Nations Development Program recently categorized Indonesia as a lower middle-income country.<sup>14</sup> In such low- and middle-income countries, the

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Key words: ART-naive individuals, HIV/AIDS, transmitted drug resistance.

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Conflict of Interest: the authors declare no potential conflict of interests.

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emergence of TDR would likely hamper efficient ART since drug resistance testing for TDR monitoring is generally not widely available at clinical sites.<sup>15</sup> It is aimed to identify the presence of HIV-1 TDR among treatment-naive individuals residing in

Jakarta, Indonesia, and also to clarify the currently circulating HIV-1 subtype/CRFs in the region.

## Materials and Methods

### Demographic characteristics of study participants

Procedures employed in this study were approved by ethical committee of Kobe University Graduate School of Medicine (approval number: 784) prior the commencement of the study. Forty-three HIV-1 infected individuals at the Sulianto Saroso Hospital in Jakarta were enrolled in this study. Written informed consent was provided by each individual prior to sample collection. Treatment-naïve status was confirmed by medical records. Peripheral blood samples were collected from each participant. Peripheral blood mononuclear cells were then isolated from samples by a density gradient centrifugation using the BD Vacutainer CPT Tube (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), subjected to DNA extraction using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany).

### HIV-1 Genotyping analysis

Amplification of HIV-1 PR and RT genes were conducted by a nested polymerase chain reaction (PCR) using the Gotaq green master mix (Promega, Madison, WI, USA) or Ex Taq (Takara Bio, Shiga, Japan) and primer sets described previously.<sup>6</sup> Primer sequences are available upon request. We carried out a limiting dilution of DNA samples, and endpoint PCR amplicon which may from the major population of virus in infected individuals were subjected to sequencing analysis using the BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, Foster City, CA, USA) and the ABI PRISM 3500 genetic analyzer (Applied Biosystems, Foster City, CA, USA). Viral sequence data were assembled and aligned using Genetyx version 10 software (Genetyx, Tokyo, Japan). The Recombinant Identification

Program (RIP) available on Los Alamos National Laboratory website ([www.hiv.lanl.gov/](http://www.hiv.lanl.gov/)) was utilized for HIV-1 subtyping. As an addition, phylogenetic analysis using a neighbor-joining (NJ) method with Kimura two-parameter model were performed by using MEGA6.2 software.<sup>16</sup> If there was an incompatibility in the results of viral subtyping between the PR and RT genes of one sample, the viral genomic fragments were considered to be derived from a recombinant virus. Detection of drug resistance-related mutations against antiretroviral drugs was carried out according to drug resistance mutations panel of the International Antiviral Society-United States of America (IAS-USA), as well as the World Health Organization (WHO) surveillance list. The presence of at least one drug resistance-related major mutation was defined as TDR.<sup>17</sup> Sequence data were deposited in the GenBank database with accession numbers MH200718 - MH200738, MH200709-MH200717, MK927045 – MK927049, and MK937919.

## Results

### HIV-1 subtyping

We successfully sequenced 21 full-length, 297-bp PR genes [corresponding to nucleotide (nt) 2253 - 2549 of a HIV-1 subtype B reference strain, HXB2 (GeneBank accession no. K03455)] and the N-terminal region of 43 RT genes (729 bp, nt 2583 - 3311). The results of viral subtyping were mostly consistent between RIP and phylogenetic analysis; however, in the case of contradictions between these analyses, the results of the phylogenetic analysis were taken (data not shown). As the results, CRF01\_AE was found to be a predominant HIV-1 subtype in Jakarta (19/26, 73.08%), followed by recombinant forms containing subtype B and CRF01\_AE genomic fragments (5/26, 19.23%) and a recombinant form containing subtype G and CRF01\_AE genomic fragments (1/26, 3.85%), and sub-

type B (1/26, 3.85%) (Figure 1). These results suggest that CRF01\_AE was the predominant CRF in Jakarta, similar to other regions in Indonesia.<sup>4-9</sup>

### Prevalence of TDR in RT and PR Genes

Identification of TDR using the drug resistance mutation panel of the IAS-USA and WHO surveillance list shown the presence of at least one drug resistance-related major mutations in 2 of 43 RT genes (data not shown). Therefore, the overall prevalence of TDR was calculated to be 4.65%. Two major mutations against NNRTIs, K103N and Y181C, were detected in peripheral blood samples derived from 2 patients, SS21 and SS41 (Table 1). These mutations affect viral susceptibilities to EFV, NVP, etravirine (ETR), and RPV (Table 1). CRF01\_AE was detected in both samples (data not shown). Despite no drug resistance-related major mutations were identified, several drug resistance-related minor mutations including M36I [amino acid substitution from methionine (M) to isoleucine (I) at position 36 in the PR gene] (85.71%), H69K (85.71%), L89M (76.19%), K20R (57.14%), and G16E (47.62%), were detected in the PR genes (Table 1). These mutations potentially affect viral susceptibilities to PIs, such as ritonavir-boosted atazanavir, ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, ritonavir-boosted indinavir, ritonavir-boosted lopinavir, nelfinavir, ritonavir-boosted saquinavir, and ritonavir-boosted tipranavir.<sup>17</sup> The detection of drug resistance-related mutations was carried out based on the drug resistance mutations list of the IAS-USA (International Antiviral Society - United States of America). Bold letters denote drug resistance-related major mutations. **1** ATV/r, ritonavir-boosted atazanavir; **EFV**, efavirenz; **ETR**, etravirine; **FPV/r**, ritonavir-boosted fosamprenavir; **IDV/r**, ritonavir-boosted indinavir; **LPV/r**, ritonavir-boosted lopinavir; **NFV**, nelfinavir; **NVP**, nevirapine; **RVP**, rilpivirine; **SQR/r**, ritonavir-boosted saquinavir; **TPV/r**, ritonavir-boosted tipranavir.

**Table 1.** Drug resistance-related mutations detected in *pol* genes encoding protease and reverse transcriptase derived from treatment-naïve individuals residing in Jakarta, Indonesia.

Gene	Mutation	Frequency (%)	Resistance to
Protease	L101V	27.3	ATV, IDV, NFV, FPV, LPV, SQR
	L33F	4.5	ATV, DRV, LPV, TPV
	K20I	4.5	ATV
Reverse transcriptase	<b>K103N</b>	6.67	EFV, NVP
	<b>Y181C</b>	6.67	EFV, ETR, NVP, RPV

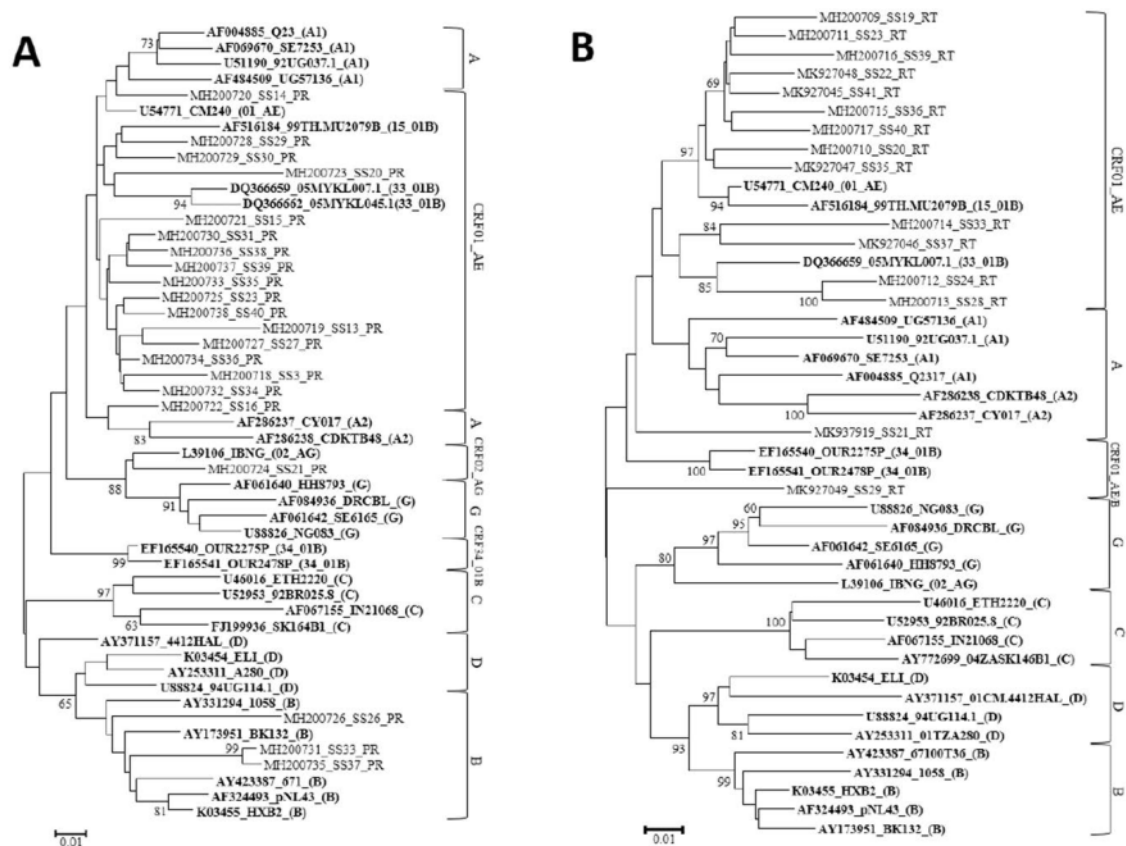
### Discussion

Viral subtyping and genotypic drug resistance analyses were combined in the present study to elucidate the genotypic characterization of HIV-1 variants circulating in Jakarta, Indonesia. Subtyping results were consistent with previous studies.<sup>4-9</sup> The CRF01\_AE was found to be a predominant CRF among HIV-infected treatment-naive individuals in Jakarta. The CRF is known to predominantly circulate in Southeast-Asian countries, including Thailand and Malaysia,<sup>18,19</sup> as well as in East-Asian countries, including Taiwan, China, South Korea, and Japan.<sup>20</sup> These findings indicate the increase of worldwide prevalence of CRF01\_AE viruses. In addition, a study in China observed faster dis-

ease progression due to HIV-1 CRF01\_AE infection.<sup>21</sup> The CRF01\_AE virus was also associated with faster decline of CD4 and higher prevalence of CXCR4-tropic variants;<sup>22</sup> however, in the present study, CD4 data was not available. Therefore, the association of CRF01\_AE infection and disease status was not clear in Indonesia. A recombinant virus containing subtype G and CRF01\_AE genomic fragments was detected. Subtype G virus is not commonly prevalent in Indonesia and other Southeast Asian countries; therefore, it might be emerged from other region of the world. Continuous surveillance studies to monitor circulating subtypes and CRFs of HIV-1 in Indonesia are required.

Unlike ADR in ART-experienced individuals which is related to prolong use of

ART and unplanned treatment interruption due to lack of adherence or inaccessible ART, TDR in ART-naive individuals is resulted from transmission of drug resistant strain.<sup>23,24</sup> Due to the occurrence of TDR, a newly HIV-1-infected individuals may carry a drug-resistant virus without yet receiving ART.<sup>15</sup> In this study, the detection rate of TDR against RT inhibitors was low (2/43, 4.65%), which was consistent to the results our previous study conducted in Surabaya, Indonesia (4.3%, 2/47).<sup>5</sup> HIV prevention trial conducted in Indonesia, Vietnam, and Ukraine (HTPN 074) revealed the presence of HIV major DRMs among 24.1% (27/112) injecting drug users in Jakarta;<sup>25</sup> thus the transmission of HIV drug resistant strain might be possible to occur, resulting in the presence of RT inhibitors



25 Figure 1. Phylogenetic tree analysis of HIV-1 pol genes encoding viral RT and PR derived from treatment-naive individuals residing in Jakarta, Indonesia. NJ tree were constructed on HIV-1 pol genes encoding protease (A) and reverse transcriptase (B). HIV-1 genomic fragments derived from subtypes A1, A2, B, C, D, and G reference strains, as well as CRF01\_AE, CRF02\_AG, CRF15\_01B, CRF33\_01B, and CRF34\_01B reference strains were included in the analysis (in bold). The sample IDs are shown as combinations of a GeneBank accession number, sample ID, and the assigned subtype or CRF of the reference strain (shown in parentheses) in that order. Bootstrap values were mentioned when the value is more than 70.

TDR among ART-naïve individuals residing in Jakarta.

Samples from SS21 and SS41 contained K103N and Y181C mutations that conferred viral resistance against EFV and NVP.<sup>17</sup> Detection of K103N as a TDR was consistent to the finding of the same mutation as the most frequent NNRTI-related drug resistance mutation found in Surabaya, Indonesia.<sup>5</sup>

Compared to studies conducted in other countries, similar results were found in China. Low TDR prevalence (3.6%; <5%), the presence of K103N, and high prevalence of CRF01\_AE in China were reported by Zhao *et al.* in 2018.<sup>26</sup> On the contrary, higher TDR prevalence was found in European countries and the United States; however, higher rate of K103N mutation was observed among Indonesian individuals recently infected with HIV-1.<sup>27,28</sup> ART expansion in Indonesia may be related with the high prevalence of K103N and Y181C, because NVP and EFV are used in the first-line ART regimens in this country. In contrast, TDR to PIs is less common, possibly due to less frequent use of the drugs in Indonesia. In the present study, no TDR against PIs was detected, while minor mutations, M36I (85.71%), H69K (85.71%), L89M (76.19%), K20R (57.14%), and G16E (47.62%), were frequently detected among 85.71% of PR genes (Table 1). These mutations have been identified as natural polymorphisms among CRF01\_AE viruses.<sup>29</sup> This result is also consistent with previous findings showing the absence of TDR against PR inhibitors in Indonesia.<sup>5</sup> The presence of minor PI mutations is considered to have no effect on therapy outcome in HIV-infected individuals. No difference was found between individuals with and without minor PI mutations in regards of time to viral suppression. Thus, PIs can be incorporated into the regimen of HIV-infected individuals with minor PI mutations when needed.<sup>30</sup>

The WHO classifies TDR into three categories: low (<5%), moderate (5-15%) and high (>15%) prevalence. When the prevalence is low, (<5%), the national ART program should function optimally. When moderate (5-15%) prevalence is detected, the WHO advises public health action, such as examining specific ART practice practices and drug quality measures for specific drug classes for which prevalence is >5%, increased support to ART programs to minimize the emergence of drug resistance in treatment and prevention programs to minimize the TDR. In addition, if high (>15%) prevalence is found, the WHO advises strong public health action, such as increased surveillance and a change in first-

line ART regimens. In our study, no TDR was detected for PIs, while low prevalence (<5%) of TDR for RT inhibitors was found in Jakarta, indicating optimal implementation of national ART program in the aforementioned region.

## Conclusion

CRF01\_AE is a predominant CRF circulating in Jakarta. In addition, as a minor CRF in Southeast Asia, recombinant variants containing subtype G and CRF01\_AE gene fragments were detected. The appearance of TDR was lower than 5%. The drug resistance-associated major mutations, K103N (6.67%) and Y181C (7.14%), were detected in RT genes, suggesting the emergence of TDR in Jakarta. It is conceivable that consider that surveillance on HIV-1 subtypes/CRFs as well as on the emergence of TDR to be required in this region.

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