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Sequence note

2018-2019 Update on the Molecular Epidemiology of HIV-1 in Indonesia

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Running head: HIV-1 epidemiology in Indonesian cities

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Abstract

The HIV-1 epidemic has continued to grow in Indonesia; however, continuous updates on the epidemiology of HIV-1 in Indonesia remain challenging because it is the biggest archipelago in the world. Furthermore, the emergence of HIV drug resistance (HIVDR) has had a negative impact on the treatment of infected individuals. In the present study, we performed HIV-1 subtyping and the detection of HIVDR in 105 HIV-1-infected individuals residing in various cities in Indonesia in 2018 - 2019. The results obtained identified CRF01_AE as the major epidemic HIV-1 strain, responsible for 81.9% of infection cases, followed by subtype B (12.4%), CRF02_AG (3.8%), CRF52_01B (1%), and a recombinants between CRF01_AE and CRF02_AG (1.0%). Major drug resistance-associated mutations against reverse transcriptase inhibitors were detected in 20% of samples. These results suggest that CRF01_AE is a major HIV-1 strain in Indonesia, while CRF02_AG is emerging. The prevalence of HIVDR in Indonesia needs to be monitored.

Key words: HIV-1 subtype, CRF01_AE, CRF02_AG, HIV drug resistance, Indonesia

Text

According to the latest 2019 report by UNAIDS, the HIV/AIDS epidemic is still regarded as a major public health burden, particularly in low and middle-income countries (LMICs), including Indonesia.[1] Approximately 640,000 (550,000 – 750,000) adults and children are now living with HIV in Indonesia, and this number is predicted to increase by 50,000 each year.[2] Antiretroviral therapy (ART) has been recommended in Indonesia as a standard treatment for HIV-1-infected individuals regardless of their CD4 T-lymphocyte count. Although ART has successfully reduced HIV-related morbidity and mortality in Indonesia, the emergence of HIV drug resistance (HIVDR) remains a challenge in long-term treatment.

HIV type 1 (HIV-1) is the major causative agent of HIV disease discovered in Indonesia, with more HIV-1 cases being reported in the Eastern part of Indonesia.[3-8] Papua and West Papua are two provinces with the highest rates of HIV-1 (1.34 - 2.41%) in Indonesia.[9] Bali, Nusa Tenggara, and Sulawesi are three islands in the Eastern part of Indonesia in which the epidemic of HIV-1 infection continues to grow due to the high numbers of men who have sex with men (MSM), injecting drug users (IDUs), and commercial sex workers in these areas.[4-6] However, there are more provinces in Indonesia without properly recorded data on HIV-1 epidemiology.

HIV-1 is divided into four subgroups: M (major), O (Outlier), N (new or non-M, non-O), and P. Group M has been identified as the most common HIV-1 infection and is classified into subtypes, circulating recombinant forms (CRFs) and unique recombinant forms (URFs). CRF-01_AE is defined as the most prevalent HIV-1 strain, accounted for 80% of CRFs in South East and East Asian countries, including Indonesia, and consistently increased in the global proportion of recombinants between 2010 and 2015.[10] Different HIV-1 subtypes and CRFs show different rates of disease progression,

immune responses, responses to ART, and/or the development of HIVDR.[11] Therefore, it is important to monitor the global and local prevalence of subtypes and CRFs for the prevention and control of HIV-1 as well as vaccine development.

Indonesia, as one of the South East Asia Region (SEAR) countries, uses the combination of 2 nucleoside reverse transcriptase (RT) inhibitors (NRTIs) and a non-NRTI (NNRTI) as the recommended first-line ART regimen.[12] Lamivudine (3TC) and nevirapine (NVP) or efavirenz (EFV) are commonly used in Indonesia as the first-line regimen representing NRTIs and NNRTI, respectively.[13] However, since the occurrence of HIVDR is inevitable, the routine monitoring of ART efficacy is necessary as part of the HIVDR surveillance program in Indonesia.

In order to evaluate current epidemic HIV-1 strains and monitor the emergence of HIVDR throughout Indonesia, we performed the genotypic characterization of viral genomes derived from HIV-1-infected individuals residing in the following locations: Aceh, North Sumatra, West Kalimantan, East Kalimantan, North Sulawesi, East Java, Bali, East Nusa Tenggara, West Papua, and Papua, which geographically cover the Eastern to Western parts of Indonesia.

Peripheral blood samples were collected from HIV-infected individuals at several cities in Indonesia (Banda Aceh, Aceh; Medan, North Sumatra; Pontianak, West Kalimantan; Samarinda, East Kalimantan; Manado, North Sulawesi; Surabaya, East Java; Denpasar, Bali; Kupang, East Nusa Tenggara; Sorong, West Papua; and Jayapura, Papua) in 2018-2019. A total of 113 samples, consisting of 3 ART-naïve and 110 ART-experienced individuals, were examined in the present study with approval from the Institutional Ethics Committees of Universitas Airlangga (approval number: 25-995/UN3.14/PPd/2013) and Kobe University Graduate School of Medicine (approval number: 784). The completion of a questionnaire was part of this study and written

informed consent was obtained from all study participants prior to their enrollment. Questionnaires were then distributed and filled in by each participant.

Ten milliliters of peripheral blood samples were collected in ethylenediaminetetraacetic acid (EDTA)-treated vacutainer tubes. Plasma was isolated from whole blood samples by centrifugation at 2,000 rpm for 10 min. DNA was extracted from the remaining whole blood sample using the QIAamp DNA blood mini kit (QIAGEN, Hilden, Germany). Viral load data was not available, but we expected low viral load for most samples under ART; therefore, we decided to amplify HIV-1 genes from whole blood samples containing lymphocytes. The HIV-1 *pol* gene encoding protease (PR) (PR gene) and RT (RT gene) as well as viral *gag* and *env* genes were then amplified from extracted DNA using the GoTaq green master mix (Promega, Wisconsin, USA) and specific primer sets corresponding to the targeted genes (Table 1). PCR conditions are available upon request. PCR products were confirmed by 1.5% agarose gel electrophoresis followed by ethidium bromide staining and visualization under UV light. The PCR products amplified at the end-point dilution of DNA templates were subjected to a sequencing analysis in order to examine the genomic fragment of the major viral population in a sample.

A sequencing analysis was performed using the BigDye Terminator v3.1 Cycle Sequencing kit and ABI PRISM3500xL genetic analyzer (Applied Biosystems, Foster City, CA, USA). Sequencing data were then compiled and aligned using Genetyx version 10 software (Genetyx, Tokyo, Japan). The sequencing data of 48 PR genes [296 base pairs (bp); nt 2253–2543], the N terminus of 40 RT genes (741 bp; nt 2571–3311), the partial fragment of 69 *gag* genes encoding Gag p24 (390 bp; nt 1633–2002), and the partial fragment of 60 *env* genes spanning the C2-V3 region (389 bp; nt 7020–7408) were obtained from 113 whole blood samples. We analyzed the similarity of

sequencing data, and if same sequence was detected from samples derived from different individuals, we suspected potential contamination among samples, and repeated the experiments from the DNA extraction to sequencing analysis for suspected samples. If same sequence was detected again, we considered it was not due to the contamination. The nucleotide sequences of the PR, RT, *gag*, and *env* genes have been registered in the GenBank database under accession numbers MT489464 – MT489511 (PR genes), MT489641 – MT489680 (RT genes), MT489512 – MT489580 (*gag* genes), and MT489581 – MT489640 (*env* genes).

HIV-1 subtyping was then performed by a phylogenetic tree analysis, jumping profile Hidden Markov Model (jpHMM)-HIV tools available on the website (http://jphmm.gobics.de/submission_hiv), and recombinant identification program (RIP) available on the HIV sequence database website (http://www.hiv.lanl.gov/). Neighbor-joining (NJ) trees with the Kimura two-parameter model were constructed using MEGA6.2 software.[6, 7] Bootstrap values (1,000 replicates) for relevant nodes were reported on a representative tree. Phylogenetic trees for the PR, RT, *gag*, and *env* genes are shown in Figure 1. In a preliminary phylogenetic tree for RT genes, MT489659_TAN_7-18_RT and MT489663_IM 2-18_RT located outside the CRF01_AE and subtype B clades (data not shown). Therefore, we searched similar sequences to them by BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi), and as the results, CRF52_01B reference strains isolated in Malaysia or Thailand, and recombinants between CRF01_AE and CRF02_AG (01_AE/02_AG recombinant) isolated in Indonesia were found. These viral genes were included in the phylogenetic tree for RT genes (Fig. 1B). Viral subtyping by RIP, jpHMM-HIV, and phylogenetic trees showed basically consistent results (data not shown); however, if different results were obtained, the viral subtype was assigned based on the results of the phylogenetic

tree analysis. In addition, if there was an incompatibility in the subtype or CRF among the PR, RT, *gag*, and *env* genes, the viral gene was considered to be from a recombinant virus.

HIV-1 viral fragments were successfully amplified from 105 out of 113 blood samples. Viral subtyping revealed that CRF01_AE (81.9%), subtype B (12.4%), CRF02_AG (3.8%), CRF52_01B (1%), and a recombinant between CRF01_AE and CRF02_AG (1.0%) were detected from samples collected from various cities in Indonesia. HIV-1 subtype and CRF distributions in various cities in Indonesia are shown in Figure 2. CRF01_AE was prominent in the population of Surabaya (21.0%; 22/105), followed by Samarinda (14.3%; 15/105), Bali (12.4%; 13/105), Manado (10.5%; 11/105), and Medan and Sorong (7.6% each; 8/105), and was detected in less than 5% of the populations of Jayapura, Pontianak, Banda Aceh, and Kupang. CRF01_AE is the main HIV-1 CRF circulating in Southeast Asia, including Cambodia, Vietnam, Malaysia, and Thailand, as well as in East Asia, such as China, Taiwan, Korea, and Japan.[14] In addition, the high prevalence of CRF01_AE in Indonesia is consistent with our previous findings obtained in Surabaya, Indonesia.[3] CRF01_AE and subtype B were the main HIV-1 CRF and subtype prevalent in Papua and West Papua, consistent with our previous findings.[7, 8] CRF02_AG was detected in Pontianak, Indonesia. Since CRF02_AG was rarely detected in Indonesia until now, the continuous surveillance of HIV-1 subtypes and CRFs appears to be required in Indonesia.

Drug resistance mutations (DRMs) were detected in the PR and RT genes based on the International Antiviral Society-United States (IAS-USA) guidelines.[15] In this study, drug resistance-associated major DRMs against NRTIs and NNRTIs were detected in RT genes derived from 8 individuals (Table 2). In contrast, major DRMs were not detected in PR genes (Table 2 and data not shown); however, several minor

DRMs against PR inhibitors were identified. Namely, among 48 PR genes, 16 (33.3%) contained G16E, 19 (39.6%) K20R, 48 (100%) M36I, 42 (87.5%) L89M/I, and 14 (29.2%) I93L. These minor mutations may appear as natural polymorphisms, and have frequently been detected in the PR genes of CRF01_AE.[15]

In conclusion, CRF01_AE viruses are still the predominant HIV-1 strains in various cities in Indonesia, which is consistent with previous findings.[3-8] In addition, subtype B, CRF02_AG, CRF52_01B, and a recombinant between CRF01_AE and CRF02_AG were detected in the present study. The emergence of CRF02_AG in Pontianak, Indonesia warrants further monitoring. Moreover, major DRMs against NRTIs and/or NNRTIs were detected in RT genes derived from 8 out of 40 individuals (20.0%), indicating that the continuous monitoring of HIVDR is required to increase ART efficiency and reduce the emergence of transmitted HIV drug resistance in Indonesia.

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Author Disclosure Statement

No competing financial interests exist.

Sequence Data

Nucleoside sequences are available under GenBank accession numbers MT489464 – MT489680.

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Table 1. PRIMERS USED FOR NESTED PCR

Genes	Primer Name	Primer locations (HXB2 numbering)	Sequences 5' - 3'
PR			
1st round	DRPR05	nt 2074 to 2095	AGACAGGYTAATTTTTTAGGGA
	DRPR02L	nt 2716 to 2691	TATGGATTTTCAGGCCCAATTTTTGA
2nd round	DRPR01M	nt 2148 to 2167	AGAGCCAACAGCCCCACCAG
	DRPR06	nt 2611 to 2592	ACTTTTGGGCCATCCATTCC
RT			
1st round	RT1L	nt 2388 to 2410	ATGATAGGGGGAATTGGAGGTTT
	DRRT4L	nt 3425 to 3402	TACTTCTGTTAGTGCTTTGGTTCC
2nd round	RT7L	nt 2485 to 2509	GACCTACACCTGTCAACATAATTGG
	DRRT6L	nt 3372 to 3348	TAATCCCTGCATAAATCTGACTTGC
gag			
1st round	H1G777	nt 1231 to 1255	TCACCTAGAACTTTGAATGCATGGG
	H1P202	nt 2352 to 2325	CTAATACTGTATCATCTGCT GCTCCTGT
2nd round	H1Gag1584	nt 1577 to 1595	AAAGATGGATAATCCTGGG
	G17	nt 2040 to 2017	TCCACATTTC CAACAGCCCTTTTT
env			
1st round	M5	nt 6858 to 6889	CCAATTCCCATACATTATTGTGCCCCAGCTGG
	M10	nt 7661 to 7632	CCAATTGTCCCTCATATCTCCTCCTCCAGG
2nd round	M3	nt 6948 to 6973	GTCAGCACAGTACAATGIACACATGG
	M8	nt 7547 to 7521	TCCTTCCATGGGA GGGGCATACATTGC

TABLE 2. APPEARANCE OF DRUG RESISTANCE-ASSOCIATED MUTATIONS IN RT AND PR GENES DERIVED FROM INFECTED INDIVIDUALS ON ART IN INDONESIA

Sample ID	Subtype/CRF[a]	Region	Drug Resistance Mutations[b]			Confer Resistance to
			NRTI	NNRTI	PI	
BB 1-18	CRF01_AE	Medan	-	**G190A**	K20R M36I H69K V82I L89M/I I93L/M	EFV, NVP
BB 2-18	CRF01_AE	Medan	-	**V181C**	G16E K20R M36I H69K V77I L89M/I I93L/M	EFV, ETR, NVP, RPV
SBY 1-18	CRF01_AE	Surabaya	**M184V**	-		ABC, FTC, 3TC
SBY 4-18	CRF01_AE	Surabaya	**M184V**	**K101E**	M36I I93L	EFV, ETR, NVP, RPV
TAN 7-18	CRF02_AG	Pontianak	-	**E138K**	L10I/V K20I M36I L63P I64L H69K L89M/I	RPV
MERUM 3-18	CRF01_AE	Manado	**D67N** **K70R** **M184V** **T215F**	**G190A**	M36I L63P H69K L89M/I I93L/M	d4T, AZT, ABC, FTC, 3TC, EFV, NVP
SOL 4-18	Subtype B	Sorong	-	**K103N** **Y188L**	L10I/V M36I	EFV, NVP, RPV
SBY 9-19	CRF01_AE	Surabaya	**M184V**	A98G **K101E** V106I **Y181C** **G190A**		ABC, FTC, 3TC, RPV, EFV, ETR, NVP

[a]HIV-1 subtypes and CRFs were assigned based on jpHMM, RIP, and phylogenetic analyses.

[b]The identification of drug resistance-associated mutations was based on the guidelines published by the IAS-USA. Major mutations are shown in bold letters.

jpHMM, jumping profile Hidden Markov Model; RIP, recombinant identification program; IAS-USA, International Antiviral Society-United States; RT gene, *pol* gene encoding reverse transcriptase; PR gene, *pol* gene encoding protease; NRTI, nucleoside RT inhibitor; NNRTI, non-NRTI; PI, PR inhibitor

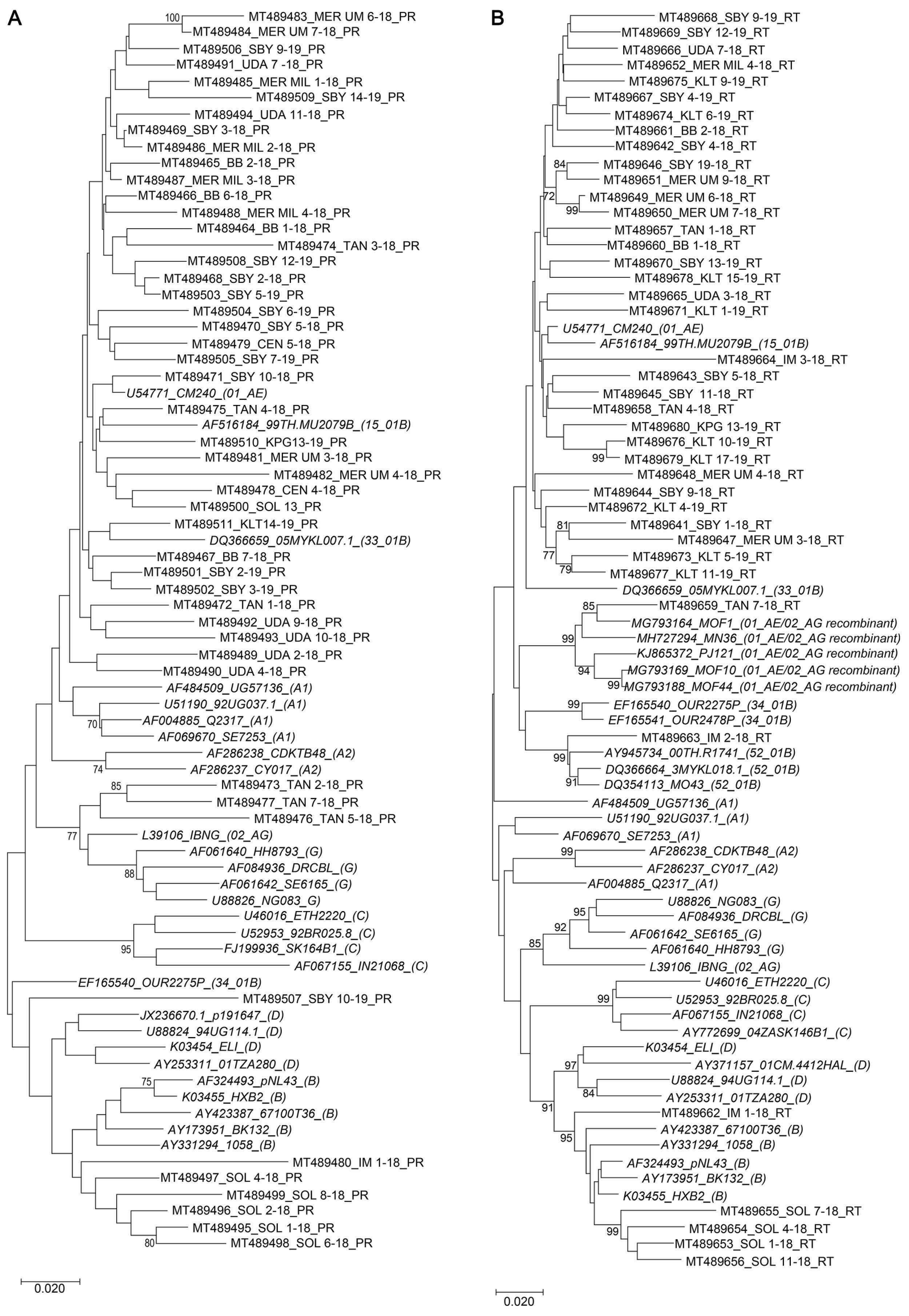
Figure legends

FIG. 1. Phylogenetic tree analysis of HIV-1 PR, RT, *gag*, and *env* gene sequences collected from various cities in Indonesia.

Phylogenetic trees were constructed for the HIV-1 PR (A), RT (B), *gag* (C), and *env* genes newly sequenced in the present study (D). The corresponding viral genes of reference HIV-1 strains representing subtypes A1, A2, B, C, D, and G as well as CRF01_AE (01_AE), CRF02_AG (02_AG), CRF15_01B (15_01B), CRF33_01B (33_01B), and CRF34_01B (34_01B) were included in the analyses (shown in italic letters). In addition, 3 CRF52_01B (52_01B) reference strains and 5 recombinants between CRF01_AE and CRF02_AG (01_AE/02_AG recombinant) were also included in the tree for RT genes (B). Sequence IDs are presented as a GenBank accession number, sample ID, or the ID of the reference HIV-1 strain, and the subtype or CRF of the strain (shown in parentheses) in that order. Bootstrap values were shown if they were >70.

FIG. 2. Geographical distribution of HIV-1 subtypes, CRFs, and recombinants in Indonesia.

HIV-1 subtyping was performed as described in the text. Circular graphs show the ratio of the subtypes/CRFs detected in each Indonesian city. The numbers of detected viral genes are shown in parentheses after the names of cities.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MT489656_SOL 11-18_RT
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MT489575_SBY 5-19_GAG
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MT489564_KLT 3-19_GAG
MT489517_SBY 6-18_GAG
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MT489563_KLT 2-19_GAG
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MT489542_MER UM 6-18_GAG
MT489523_SBY 19-18_GAG
MT489532_SOL 14-18_GAG
MT489548_UDA 5-18_GAG
MT489557_BB 5-18_GAG
MT489553_UDA 11-18_GAG
MT489513_SBY 3-18_GAG
MT489580_SBY 13-19_GAG
MT489520_SBY 9-18_GAG
MT489577_SBY 8-19_GAG
MT489543_MER MIL 2-18_GAG
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MT489569_KLT 12-19_GAG
MT489567_KLT 6-19_GAG
MT489515_SBY 4-18_GAG
MT489541_MER UM 5-18_GAG
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MT489526_SOL 6-18_GAG
MT489527_SOL 8-18_GAG
MT489524_SOL 1-18_GAG
MT489529_SOL 11-18_GAG

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AY173951_BK132_(B)
AY423387_67100T36_(B)
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MT489613_SOL 7-18_ENV
MT489614_SOL 8-18_ENV
MT489633_SBY 10-19_ENV
MT489588_CEN 2-18_ENV
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MT489612_SOL 6-18_ENV

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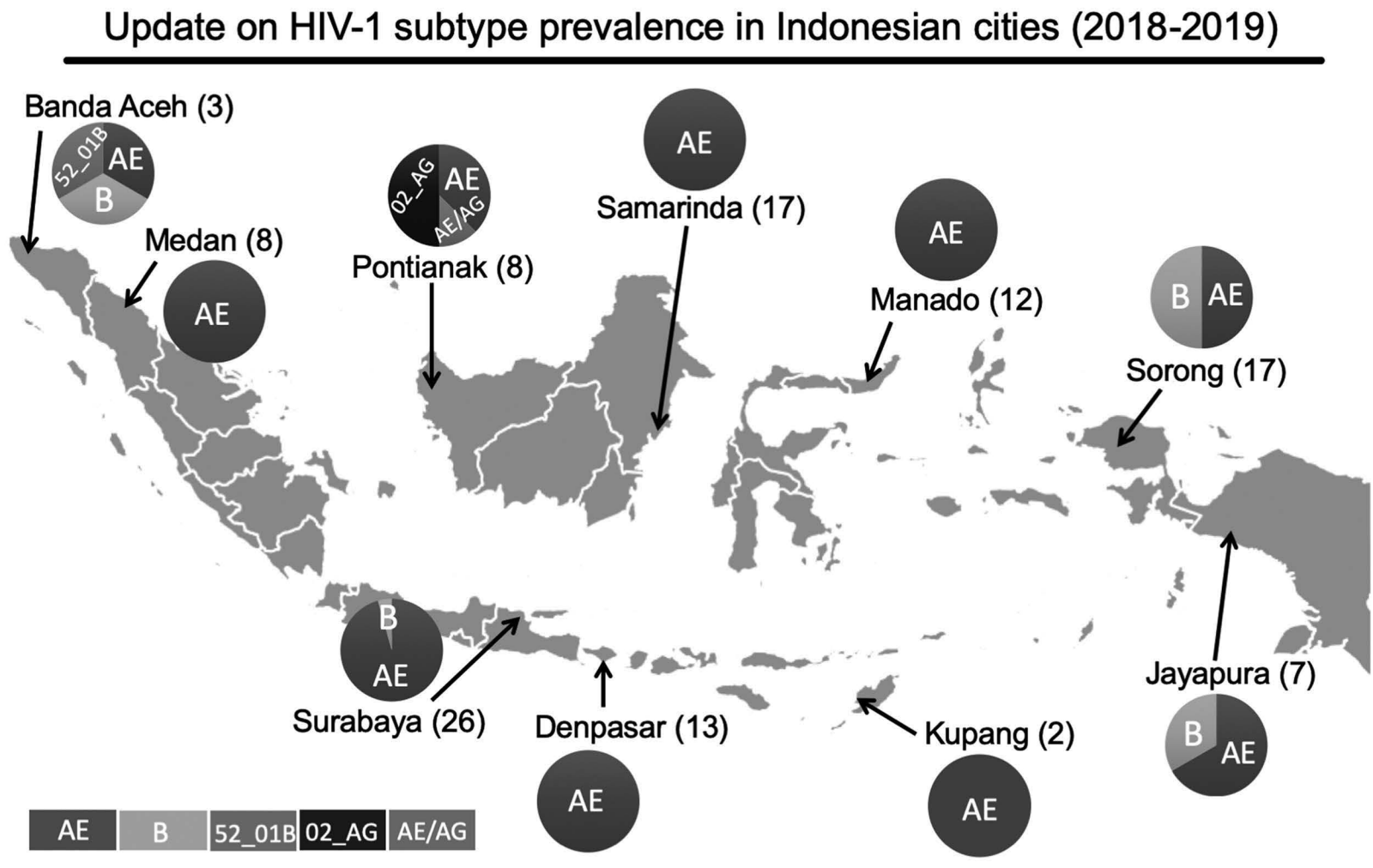
Update on HIV-1 subtype prevalence in Indonesian cities (2018-2019)
Banda Aceh (3)
52_01B
AE
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Medan (8)
AE
02_AG
AE
AE/AG
Pontianak (8)
AE
Samarinda (17)
AE
Manado (12)
B
AE
Sorong (17)
B
AE
Surabaya (26)
Denpasar (13)
AE
Kupang (2)
AE
Jayapura (7)
B
AE
AE
B
52_01B
02_AG
AE/AG