High rates of hepatitis B, hepatitis C and human immunodeficiency virus (HBV, HCV, HIV) infections and their uncommon HBV genotype/subtype and HCV subtype distributions among transgender individuals in Surabaya, Indonesia

Alfonsus Adrian Hadikusumo, Takako Utsumi, Mochamad Amin, Siti Qamariyah Khairunisa, Anittaqwa Istimagfirah, Rury Mega Wahyuni, Maria Inge Lusida, Soetjipto, Edhi Rianto, Juniastuti, and Yoshitake Hayashi

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High Rates of Hepatitis B, Hepatitis C and Human Immunodeficiency Virus (HBV, HCV, HIV) Infections and Their Uncommon HBV Genotype/Subtype and HCV Subtype Distributions among Transgender Individuals in Surabaya, Indonesia

Alfonsus Adrian Hadikusumo¹, Takako Utsumi²,³*, Mochamad Amin², Siti Qamariyah Khairunisa², Anittaqa Istimagfirah², Rury Mega Wahyuni², Maria Inge Lusida¹,², Soetjipto¹,², Edhi Rianto¹, Juniastuti¹,², and Yoshitake Hayashi³

¹ Faculty of Medicine, Airlangga University, Surabaya, Indonesia;
² Indonesia-Japan Collaborative Research Centre for Emerging and Re-emerging Infectious Diseases, Institute of Tropical Disease, Airlangga University, Surabaya, Indonesia; and
³ Center for Infectious Diseases, Kobe University Graduate School of Medicine, Kobe, Japan

Running title: HBV, HCV and HIV among transgender in Indonesia

*Correspondence: Dr Takako Utsumi, Center for Infectious Diseases, Graduate School of Medicine, Kobe University, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017 Japan. E-mail: tutsumi@people.kobe-u.ac.jp. Phone: +81-78-382- 5700/Fax: +81-78-382-5719

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内海孝子、インドネシア国スラバヤ市ムリオレジョ通り 60115、神戸市中央区
楠町 7-5-1

林祥剛、神戸市中央区楠町 7-5-1
SUMMARY

Transgender people are at high risk of sexually transmitted viruses such as hepatitis B virus (HBV) and human immunodeficiency virus (HIV). Moreover, Indonesia has a moderate to high rate of HBV infection and a rapid epidemic growth of HIV. Because hepatitis C virus (HCV) can co-occur with HBV and HIV, it was also evaluated in this study. Ten of 107 individuals (9.3%) were Hepatitis B surface antigen (HBsAg) positive and/or HBV DNA positive, whereas nineteen of 101 individuals (18.8%) with negative HBsAg were Hepatitis B core antibody (anti-HBc)-positive. Seven of 107 individuals (6.5%) were anti-HCV positive, and sixteen of 100 tested samples (16%) were HIV positive. Genotype and subtype analyses of all ten HBV DNA (six HBsAg positive and four anti-HBc positive) strains showed that three were HBV genotype/HBsAg subtype C/adrq+, one was C/adw2, and five were B/adw2. The HCV subtype distribution showed that 33.3% were HCV-1b, and 66.7% were HCV-3k (n=6). These distributions differed from those found in the general population of Surabaya, Indonesia. The HIV subtype analysis showed that, interestingly, a high prevalence of HIV, with possible recombinants of CRF01_AE and subtype B, were found.

INTRODUCTION

People who identify as transgender commonly have risky sexual behaviors and are at an increased risk of acquiring sexually transmitted viruses (1). Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) are among the viruses that can lead to severe chronic infections (2). Because hepatitis C virus (HCV) can co-occur with HBV and HIV, it might also be sexually transmitted (3), especially among people with multiple sexual partners although to a much lesser extent than HBV (2).

Indonesia is a country with a moderate to high (6%-9%) rate of HBV infection (4). According to the report from the United Nations Program on HIV/AIDS (UNAIDS),
Indonesia has also shown a rapid epidemic growth of HIV with the estimated number of people living with HIV from 12,000 in 2001 to 380,000 in 2011 (approximately 32-fold) (5,6). The prevalence of HCV in the general population during this timeframe in Indonesia was 2.1%-2.3% (7,8).

HBV and HCV genotypes show marked geographic and ethnic distributions. HBV isolates of different genotypes and subtypes show different geographical distributions, virological characteristics, and (possibly) clinical outcomes (9,10). Genotypes B and C (HBV/B and HBV/C, respectively) predominate in Asia and Indonesia in particular (11,12). Indonesia is a multiethnic country. We previously reported the distribution of the genotypes and subtypes of HBV across several geographical areas in Indonesia (9,13). In addition, we reported the prevalence of each HCV subtype, including HCV subtype 1c (HCV-1c), among various clinical populations in Indonesia.

Because the data regarding the genomic characterization of HIV, HBV, and HCV are scarce with regard to the global transgender population (1,14), this study aimed to characterize the HBV HCV, and HIV subtypes circulating among this community in Surabaya, Indonesia at the molecular level.

MATERIAL AND METHODS

Serum Samples

A total of 107 sera were collected from a group of transgender individuals under the supervision of a health center in the port area in Surabaya, Indonesia in 2012. Health center firstly recognized transgender from their appearance and interview. They were then asked to join the community supervised by the health center to be regularly followed up to detect sexual transmitted diseases. In this study, questionnaire is used to gain information of the identity, orientation and partners, as well as history of previous infection. All of them (100%
were transgender women who were born as men but later identify themselves as women. They didn’t have history of previous HBV, HCV, and HIV infections. All of the sera were stored at -80°C before they were examined at the Institute of Tropical Disease, Airlangga University. The ethical clearance for this study was obtained from the Ethics Committee of the Faculty of Medicine Airlangga University and Kobe University, Japan. All of the participants signed an informed consent document and volunteered for this study.

**HBV serological tests, DNA extraction, and PCR amplification**

The sera were screened for HBsAg using a reverse passive hemagglutination assay (Mycell II HBsAg; Institute of Immunology, Tokyo, Japan) and Anti-HBc using passive hemagglutination (Mycell II anti-rHBc; Institute of Immunology).

A part of the S gene from the samples that were HBsAg or Anti-HBc positive was amplified using PCR for HBV DNA detection. HBV DNA was extracted from 200 µL serum using a DNA extractor kit (QIAamp DNA Blood Mini Kit; QIAGEN, Tokyo, Japan). The presence of HBV DNA was assayed using PCR with P7 (5’-GTGGTGGACTTCTCTCAATTTC-3’, nucleotides [nt] 256 to 278) and P8 (5’-CGGTAWAAAGG GACTCAMGAT-3’, nt 796 to 776) primer pairs to detect the presence of the S gene (nt 256 to 796). When the PCR amplification was negative, a second-round (nested) PCR was conducted using primers HBS1 (5’-CAAGGTATGTTG CCCGTGGTGG-3’, nt 455 to 474) and HBS2 (5’-AAAGCCCTGCGAACCACCTGA-3’, nt 713 to 694) (9). Both first and second round PCRs were performed, each of which consisted of a 5-min denaturation at 94°C, followed by 40 cycles of 1 min at 94°C, 1 min at 55°C and 2 min at 72°C (15).

**HCV serological test, RNA extraction and RT-PCR amplification**

The presence of anti-HCV antibody among the sera was also detected using the reverse particle hemagglutination method (Ortho HCV Ab PA test II; Ortho-Clinical Diagnostics, Tokyo, Japan).
Sera testing positive for the anti-HCV antibody were further analyzed for HCV RNA. HCV RNA was extracted from 140 μl of serum using a commercially available kit (QIAamp Viral RNA kit: Qiagen, Tokyo, Japan).

To amplify the NS5B region of the HCV genome, the extracted RNA was reverse-transcribed and amplified using SuperScript One-Step RT-PCR (Invitrogen, Tokyo, Japan). PCR was performed using Platinum Taq DNA polymerase (Invitrogen Life Technologies, Carlsbad, CA, USA). The reaction was initially performed at 45ºC for 30 min for RT and at 94ºC for 2 min, followed by the first-round of PCR over 40 cycles. Each cycle consisted of a pre-denaturation at 94ºC for 3 min, denaturation at 94ºC for 30 seconds, annealing at 56ºC for 40 seconds, and an extension at 72ºC for 1 min using the outer primers F1 (5'-CAATWSM-MACBACCATCATGGC-3', nt 7999-8020, +) and R1 (-5' -CAGGARTTRACTGGAGTGTG-3', nt 8805-8825, -). The second round of PCRs was performed under the same conditions used to amplify the HCV genome using the inner primers F2 (5'-ATGGGHHSBKCMTTYGGATTCC-3', nt 8159-8181, +) and R2 (5'-CATAGCNTCCGTGAANGCTC-3', nt 8611-8630, -) (16). All of the PCRs were performed using Hot Star Master Mix (Qiagen, Tokyo, Japan).

**Anti-HIV antibody test, HIV type 1 (HIV-1) genomic fragment amplifications**

One hundred sera samples were screened for HIV using three methods: a rapid diagnostic test (HIV 1/2 one step rapid test; Zhejiang Orient Gene Biotech Co. Ltd., Zhejiang, China) followed by a double antigen/antibody sandwich Enzyme Linked Immunoassay (EIA; HIV 1/2/O Antigen/Antibody; ACON Laboratories Inc., San Diego, USA) and an immunochromatographic assay system (MONO 1/2 HIV Test; Shanghai Huaguan Biochip Co. Ltd., Shanghai, China).

The samples with anti-HIV antibody positive were amplified their proviral DNAs. They were extracted from peripheral blood mononuclear cells (PBMC) using (QIAamp DNA
Blood Mini Kit; QIAGEN, Tokyo, Japan). For the amplification of viral \textit{pol} gene fragment, UNIPOL 5; \texttt{5'-TGGGTACCAGCACACAAAGGAATAGGAGGA-A-3'} (nt 4152 to 4183) and UNIPOL 6; \texttt{5'-CCACAGCTGATCTCTGCTTCTCTGGTAATAGA-CC-3'} (nt 4934 to 4901) were used for the first PCR, while UNIPOL 1; \texttt{5'-AGTGGAT-TCATAGAACAGAAGT-3'} (nt 4470 to 4492) and UNIPOL 2; \texttt{5'-CCCCTATTCCTcccccttt-CTTTAAA-3'} (nt 4806 to 4781) were used for nested PCR. The first PCR of \textit{pol} gene consists of one cycle of denaturation for 5 min at 94°C; 35 cycles of 1 min at 94°C for denaturation, 1 min at 45°C for annealing and 1 min at 72°C for extension; and a final extension cycle of 5 min at 72°C. For the second PCR of \textit{pol} gene amplification, the annealing temperatures were changed to 50°C, 55°C, and 60°C respectively (6). In addition, for amplification of the viral \textit{gag} gene fragment, H1G777; \texttt{5'-TCACCTAGAACTTTGAATGCATGGG-3'} and H1P202; \texttt{5'-CTAATACTGTATCATCTGCTC-CTGT-3'} were used for the first PCR, while H1gag1584; \texttt{5'-AAAGATGGATAATCCTGGG-3'} and g17; \texttt{5'-TCCACATTTCACACAGCCCTTTTTTT-3'} were used for nested PCR. The PCR conditions were as follows. For the 1st PCR of \textit{gag} gene amplification, one cycle of 3 min at 95 °C for denaturation; 35 cycles of 1 min at 95 °C for denaturation, 1 min at 58°C for annealing and 1 min at 72°C for extension; and a final extension cycle of 3 min at 72°C were carried out. For the nested PCR of \textit{pol} gene amplification, the annealing temperatures were changed to 49.4 °C.

\textbf{Sequence and phylogenetic analysis}

The nucleotides sequences of the amplified fragments of HBV, HCV, and HIV were determined using the BigDye Terminator v3.1 Cycle Sequencing kit with an Applied Biosystems 3500xL Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) (9,17,18). The sequences were compared with those from the international DNA databank (DDBJ/EMBL/GenBank).
The HBV subtypes were deduced based on the predicted amino acid sequences of HBsAg (12,19). HBV subgenotypes were determined based on the homologies (>96%) in the S gene using Genetyx-Win v10.0 (Genetyx Corporation, Tokyo, Japan) and phylogenetic analysis.

HCV subtypes were determined by the homologies of the NS5B region. When a subtype assignment was unable to be completed because of the lack of NS5B amplification, the nt sequences of the 5’ UTR were determined and compared with the consensus sequence motifs for each of the major genotypes reported previously (20,21). When the sequence of an HCV clone completely matched the consensus motifs of a major genotype, the HCV clone was assigned a genotype (e.g., HCV type 1) (22).

HIV-1 subtyping was conducted using the Recombination Identification Program (RIP) available at the website of the HIV sequence database (http://www.hiv.lanl.gov/).

The phylogenetic analysis of HBV, HCV, and HIV-1 was conducted using neighbor-joining (NJ) trees with the Kimura Two parameter model were constructed using MEGA6.2 software, after multiple alignment using the Clustal W algorithm and manual editing (23,24).

RESULTS

Samples

Peripheral blood samples were collected from 107 transgender individuals (mean age: 33.4 years old; age range: 19-60 years), consisting of 81 Javanese, 16 Maduranese, 7 other ethnicities (the descent of the ethnicities was carefully documented for three previous generations, both paternally and maternally), and 7 unknown. All samples (100%) were collected from transgender whose partners were men. None of the participants had a previous history as intravenous drug users (IVDUs) or of any other blood transmitted contact. This data was acquired from questionnaire and interview. The primary risk factor for infection among these individuals is sexual intercourse.
HBV infection among transgender individuals in Indonesia

The sero-epidemiological tests revealed that six of the 107 individuals (5.6%) were HBsAg positive; nineteen of 101 (18.8%) who were HBsAg negative were also anti-HBc positive (Table 1). In this study, we define HBV infection as those with HBsAg and/or HBV DNA positive. Ten HBV DNA positive samples (9.3%) were found, including six HBsAg positive samples and four HBsAg negative samples with anti-HBc positivity. Based on the homology of the reported isolates in the DDBJ/EMBL/GenBank, six were genotype B; interestingly, however, the other four were genotype C, which is uncommon in Surabaya. Nine samples were analyzed to determine the subtypes. Five of the nine isolates belonged to the genotype/subtype B/adw2; one belonged to C/adw2, and three belonged to C/adrq+ (Figure 1 and Table 2). In addition, one sample could not be analyzed because the sequence was not long enough.

Regarding the subgenotype of the HBV, the genotype C isolates (4/4) make a separate cluster from those reported that do not belong to C1-C16. Those with the genotype B belong to subgenotype B3. Two samples could not be analyzed because their sequences were not long enough (Figure 2).

HCV infection among transgender individuals

Seven of 107 individuals (6.5%) were anti-HCV positive (Table 1). HCV RNA was detected in all anti-HCV positive samples. The analysis of the 6 HCV RNA isolates showed that 2 were subtype 1b, and the other four were subtype 3k (Figure 3 and Table 2). One sample could not be analyzed because the sequence was not long enough.

HIV infection among transgender individuals

Sixteen of the 100 samples tested (16%) were anti-HIV positive (Table 1). Fifteen of sixteen samples were successfully amplified and went for sequence analysis. Eleven of the 16 samples (Figure 4) were positive in the pol region and other twelve samples were positive in
the \textit{gag} region. The viral subtype acquired from the RIP program showed that 11 of 11 (100\%) \textit{pol} and 8 of 12 \textit{gag} (66.7\%) (Figure 4) gene fragments were subtype CRF01\_AE while the other four (33.3\%) \textit{gag} gene fragments turned out to be subtype B (strains no. GAG TG 101, 105, 106, and 111). There were 2 possible recombinant strains (GAG TG 106 and 111) detected with subtype CRF01\_AE detected in \textit{pol} region and subtype B detected in \textit{gag} region.

**DISCUSSION**

Few data are available regarding the prevalence of viral sexually transmitted infections (STIs) including HBV and HIV among transgender individuals in Indonesia. However, several data resources exist regarding the prevalence of HBV and HIV among the general population in several parts of Indonesia (6,9,13,15,25).

Although the prevalence of chronic HBV infection has decreased over the years, an estimated of 240 million people have chronic HBV infection worldwide (26). The prevalence of HBV infection varies markedly across different geographical areas of the world. Indonesia is characterized by an intermediate to high HBV rate, and the prevalence of HBsAg has been estimated to be from 6\%-9\% in the general population (4). Hepatitis B vaccine has been available since 1982 and recommended to use worldwide by the WHO in 1992, while the Indonesian government started the national vaccination program in 1997. Individuals born before 1997 are not as thoroughly vaccinated as those born after 1997. Hence, transgender in this population has higher prevalence of HBV infection as compared to the individuals in the program. Approximately 5.6\% of the sample taken from transgender people in Surabaya, Indonesia, were HBsAg positive, or 10 (9.3\%) HBV DNA positive (including four with HBsAg negative and anti-HBe positive). The prevalence of HBV infection among transgender individuals is comparable with that of the general population. Four of nineteen
samples (21%; Table 1) showed occult HBV infection; for this reason, we strongly recommend that the anti-HBc antibody test be used as a complement to the HBsAg test to routinely screen for HBV.

As shown in Figure 2, the HBV genotype C isolates make a separate cluster from subgenotypes C1 to C16. There’s a possibility that these isolates belong to other than C1 to C16 subgenotypes. Further analysis is needed to confirm it. Other isolates belong to subgenotype B3. This is in accordance with previous studies that most of Indonesian HBV especially among Javanese are mostly B3 (27).

Our previous report revealed that more than 90% of the samples from the general population, chronic liver disease patients, and those on maintenance hemodialysis in Surabaya, belong to the genotype B and subtype adw (13), which is similar to the results found in other parts of Java Island (10,25), whereas genotype/subtype C/adrg+ were mostly found in the most eastern region of Indonesia (in the Papuan ethnic group) (9,25,28). This study showed at least 30% (3/9) had C/adrg+, and 2 of them were Maduranese. Further study is needed to confirm this situation, since tested population is very small.

Differences in the rates of HCV genotypes/subtypes exist throughout the world. We performed seroepidemiological and molecular epidemiological analyses of HCV among several population groups in Surabaya, Indonesia (18,21,22,29,30). The rates of anti-HCV antibodies were 2.3%, 76.3% and 64.7% in healthy blood donors, patients on maintenance hemodialysis, and patients with hepatocellular carcinoma (HCC), respectively. Another study reported an HCV prevalence of 2.1% in the general Indonesian population (31). Interestingly, an HCV infection rate as high as 6.5% was found among transgender people in Surabaya, Indonesia; however, HCV is less likely to be sexually transmitted. Certain mechanisms involved in the sexual transmission of HCV, particularly among partners who engage in
habits associated with a high risk of virus transmission, might play a role in this high rate of HCV infection among transgender individuals (21,32).

Although the chance of sexually transmitting HCV is less than 5%, this risk might be increased by specific sexual habits often correlated with the transgender community, such as multiple sexual partners, anal sex, and traumatic sex (33,34,35,36). The transmission risk correlated with anal sex is much higher because it is more likely to cause injury (36).

Interestingly, the subtype distributions of HCV among transgender individuals were 66.6% and 33.3% for HCV-3k and HCV-1b, respectively. These rates might be the highest for HCV-3k reported in Indonesia to date. HCV-2a was previously reported as the most common (52%) among the HCV clones obtained from blood donors in Indonesia, followed by HCV-1b (15%), HCV-1a (7%), and HCV-1c (7%), a unique Indonesian subtype (22). In a more recent study of patients with chronic liver disease, Utama et al. reported that HCV 1b (47.3%) was the most prevalent, followed by subtypes 1c (18.7%), 3k (10.7%), 2a (10.0%), 1a (6.7%), 2e (5.3%), 2f (0.7%) and 3a (0.7%) (37). Among people with HCV-HIV co-infection in Surabaya, those who are positive for anti-HCV antibodies showed HCV-1a (31.5%) as the predominant subtype, followed by 3a (23.3%), 1c (10.9%), 1b (9.6%), 3k (4.1%), 2a (1.4%), 4a (1.4%), and genotype 1 (16.4%) (19). Of those who have HCV-HIV co-infection but are negative for anti-HCV antibodies, 26 individuals (38.2%) had HCV RNA, with HCV-3a being the most prevalent subtype (50%), followed by 3k (23.1%), 1c (15.4%) and 1b (11.6%).

The distribution of various genotypes/subtypes showed geographic variation. Genotype 3 originated from and is mostly found in South Asia (38). It accounts for more than 70% of the isolates in India. The distribution of HCV genotypes/subtypes also reflects the route of transmission. We found a relatively high prevalence of genotype 3, including 3k, among people with sexually transmitted HIV-HCV co-infection (18). Related to these results, the high prevalence of genotype 3 in our study was due to sexual activity.
The prevalence of HIV in Indonesia ranges from 0.3%-0.7%, which is below the global prevalence range of 0.7%-0.8% (39,40). However, this low prevalence is because of the uneven distribution of HIV cases in Indonesia. The number of HIV cases in East Java, where Surabaya contributes the largest percentage, is the second highest number in Indonesia after Jakarta (the capital city) (41,42). The prevalence of HIV in our study is remarkable because it exceeds the high (12%) prevalence of HIV among female sex workers in Surabaya (6). Genomic fragment of CRF01_AE has been identified as the predominant HIV-1 subtype in South East Asia, including Malaysia, Thailand, and Taiwan (43,44,45) as well as Jakarta, Surabaya and Bali of Indonesia (6,46). Our results were consistent with previous findings. Remarkably, based on RIP and phylogenetic tree analysis for both pol and gag gene (Figure 4), two samples were identified as subtype B, and the other two were detected as subtype CRF01_AE in pol region, but subtype B in gag region. The diversity of genotypes distribution in these samples is predicted as newly unique recombinant. This result is similar to the previous study of subtype CRF54_01B from Malaysia (47), whereas as reported before, B subtype isn’t commonly found among Indonesian. The detection of various subtypes and recombinants in this study indicate the high diversity of the prevalence of HIV-1 in Surabaya, Indonesia.

We found a high prevalence (9.3%) of HBV infection among transgender individuals in Surabaya, Indonesia. This rate was as high as those among the adult population in Indonesia. Interestingly, 33.3% were HBV C/adrq+ and 67% of them were Maduranese. C/adrq+ was uncommon among the general population in Surabaya. Although HCV is less frequently sexually transmitted, we found that 6.5% of the sample was HCV infected. Interestingly, HCV-3k was the predominant subtype. Sexual habits that deviate from the norm are associated with a high risk of HCV infection. A very high prevalence of HIV was also found among transgender individuals. HIV subtype CRF01_AE was the predominant
isolates. Because of these high rates of HBV, HCV, and HIV infection among transgender people, we strongly recommend routine screenings for HBV, HCV, and HIV.

Acknowledgements

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Conflict of interest None to declare

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FIGURE LEGENDS

**Figure 1.** Multiple alignment of amino acid sequences of HBsAg (positions 121 to 180) of HBV isolates from transgender people, Indonesia (code TG; shown in bold) and those from international DNA data bank (indicated with the accession numbers and countries of origin; genotypes, subgenotypes and subtypes are also indicated).

**Figure 2.** Phylogenetic analysis of HBV isolates from transgender people, Indonesia (shown in bold, black letter with asterisk) and those from international DNA data bank (indicated with the subgenotype and accession number), on the basis of the S region.

**Figure 3.** UPGMA phylogenetic analysis of HCV isolates from transgender people, Indonesia (shown in bold, black letter with asterisk) and those from international DNA data bank (indicated with the accession numbers and subtypes), on the basis of partial NS5B region sequences. The genotypes and subtypes are indicated on the branches.

**Figure 4.** Phylogenetic analysis of HIV-1 *pol* (A) and *gag* (B) gene sequences from transgender people, Indonesia (code TG; shown in bold, black letter with asterisks) and reference strains of HIV-1 subtypes (shown in black). Phylogenetic trees were generated for newly sequenced HIV-1 *pol* and *gag* genes together with the corresponding viral gene of reference HIV-1 strains representing subtype A1 (A1), subtype A2 (A2), subtype B (B), subtype C (C), subtype D (D), subtype G (G), CRF01_AE (01_AE), CRF02_AG (02_AG), CRF15_01B (15_01B), and CRF33_01B (33_01B). Bootstrap values are shown when the values are > 70.
Table 1 Prevalence of HBsAg, Anti-HBc antibodies, Anti-HCV antibodies and Anti-HIV antibodies among transgender people in Indonesia

<table>
<thead>
<tr>
<th>Serological tests</th>
<th>No. positive/no. tested (%)</th>
<th>No. positive HBV DNA or HCV RNA / no. tested</th>
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<tbody>
<tr>
<td><strong>Hepatitis B</strong></td>
<td></td>
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<tr>
<td>HBsAg</td>
<td>6/107 (5.6%)</td>
<td>6/6‡</td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>19/101 (18.8%)†</td>
<td>4/19‡</td>
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<tr>
<td><strong>Hepatitis C</strong></td>
<td></td>
<td></td>
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<tr>
<td>Anti-HCV</td>
<td>7/107 (6.5%)</td>
<td>7/7</td>
</tr>
<tr>
<td><strong>HIV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HIV</td>
<td>16 / 100 (16%)</td>
<td>-</td>
</tr>
</tbody>
</table>

† A total of 101 samples with HBsAg negative were tested for anti-HBc.
‡ A total of 10 HBV DNA were detected among transgender persons with HBsAg or anti-HBc positive.
Table 2 Prevalence of HBV genotypes/ subtypes and HCV subtypes among transgender people in Indonesia

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<tbody>
<tr>
<td></td>
<td>HBV</td>
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<tr>
<td></td>
<td>9 isolates†</td>
<td>B/ adw2</td>
<td>5</td>
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<td></td>
<td></td>
<td>HCV-3k</td>
<td>4</td>
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</table>

†One HBV DNA isolate did not show good sequence result.
‡ One HCV RNA isolate did not show long enough sequence to be analyzed.

No person was co-infected with HBV and HCV.
Fig. 1. Hadikusumo et al.
Fig. 2. Hadikusumo et al.
Fig. 3. Hadikusumo et al.