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Original article

# Dual antibody and antigen tests for HIV detection among Indonesians

*Laura Navika Yamani[1,2], Dwi Wahyu Indriati[2,3], Zayyin Dinana[2], Renaldy Raditya Indrawan[2], Erni Astutik[1], Yasmin Nihayatun Nadzifah[2], Nasronudin[4], Siti Qamariyah Khairunisa[2]*

[1]Department of Epidemiology, Biostatistics, Population Studies and Health Promotion, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia; [2]Research Center on Global Emerging and Re-emerging Infectious Diseases, Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia; [3]Department of Health, Faculty of Vocational Studies, Universitas Airlangga, Surabaya, Indonesia; [4]Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

**Abstract.** *Background and aim:* Low-cost, simple, and accurate tests for screening and diagnosis of human immunodeficiency virus (HIV) are essential to control transmission in resource-limited settings such as Indonesia. Combined antibody and antigen detection assays have been widely used for initial screening. Our study aimed to describe the detection patterns of HIV antibodies and p24 antigen among HIV patients and healthy individuals in Indonesia. *Methods:* We conducted a case-control study involving 262 participants, consisting of 131 HIV-positive individuals and 131 HIV-negative controls. Antibody detection was performed using a rapid test, and p24 antigen was detected by ELISA. *Results:* Antibodies were detected in 97.7% of HIV-positive individuals, whereas antigen was detected in 25.2%. No antibodies were detected in healthy controls, although 3.1% showed antigen positivity but were PCR-negative, suggesting possible false positives or early seroconversion. Antibody results were not influenced by age, sex, marital status, ARV use, or transmission route. In contrast, antigen detection was associated with ARV use, treatment duration, and transmission route. *Conclusions:* These findings highlight the complementary roles of antibody and antigen tests in different phases of infection. While antibody tests remain robust for screening, further exploration is warranted on the potential utility and limitations of p24 antigen detection in early infection or in populations with recent exposure. (www.actabiomedica.it)

**Key words:** HIV, antibody, antigen, rapid test, ELISA, Indonesia

## Introduction

Human Immunodeficiency Virus or commonly known as HIV is one of the public health problems that still threatens many countries, including Indonesia. One of the consequences of HIV is a chronic immune system disease called acquired immunodeficiency syndrome (AIDS) because virus works by attacking the human immune system (1). HIV is a virus that can be spread through a several of human behaviours, including sexual intercourse (heterosexual or homosexual), sharing of needles by injecting drug users, or improper use of syringes (non-sterile equipment) and also can be spread by perinatal or mother-to-child transmission. According to HIV cases in global data, in 2021, more than 38.4 million (33.9 million – 43.8 million) people in the world are living with the HIV virus, with a total of more than 40.1 million (33.6 million – 48.6 million) have died from AIDS-related illnesses since the start of the

epidemic. About 1.5 million (1.1 million to 2 million) people will be newly infected with HIV in 2021 (2). According to the March 2022 report of the Indonesian Ministry of Health, the number of people living with HIV in Indonesia has exceeded 543,100 and 160,249 (41%) of them are taking antiretroviral therapy (3). Currently in Indonesia, the most HIV virus infections are found in DKI Jakarta, Java, and Papua. The HIV epidemic has a different character in each region of the world. This difference in characteristics is due to the widespread prevalence and variety of HIV subtypes worldwide (4,5). AIDS is caused by HIV-1, which is its genetic diversity that can lead to a diversity of viruses that produce new infectious pandemics (6). HIV-1 can be divided into three groups including group M (main), N (new), and O (outlier) (7,8). Group M is the cause of the world's frequent HIV epidemics. Group M is divided into various subtypes, namely subtypes A – K. Among those various subtypes, there is a combination of subtypes, namely the Circulating Recombinant Form (CRF) (9,10). HIV infection into the blood may lead to further infection of HIV-infected patients with viruses, bacteria and protozoa, resulting in AIDS reproduction (11,12). There is no cure for HIV/AIDS, but medications can control the infection and prevent disease progression (13) Therefore, detection of HIV infection is important for early diagnosis, reducing transmission and improving health outcomes (14). A laboratory determination is used as a diagnostic test for HIV infection. Centers for Disease Control and Prevention (CDC) recommends that laboratories conduct initial testing with an FDA-approved HIV antigen/antibody (Ag/Ab) immunoassay. Various screening methods that can be done include the rapid diagnostic test (RDT), Enzyme-Linked Immunosorbent Assay (ELISA), and the western blot (WB) method. The RDT and ELISA method are an effective screening test method to detect HIV antigen and antibodies. Materials used for HIV examination are blood, urine, and oral cavity fluid. In recent years, the primary method of HIV testing has shifted from ELISA to RDT, especially in resource-limited settings. In Indonesia, this shift is relevant due to the vast geographical landscape and many rural areas which has limited access to advanced laboratory facilities. RDTs is suitable for community-based testing or mobile clinics since it is easy to use, giving rapid results and no requirement of highly trained personnel or advanced laboratory infrastructure. However, the diagnostic performance of RDTs is a matter of concern. Although there is an available RDT method for detecting antigen and antibody at the same time but in Indonesia, the newest guideline still recommends RDT detecting antibody for initial testing of HIV. In this study, the performance of RDT and ELISA for HIV antibody and antigen detection was evaluated, respectively, for plasma samples derived from HIV-infected individuals and healthy volunteers. Our study also concerned the sensitivity and specificity of two methods by compared with polymerase chain reaction (PCR) results. The results of tests were suspected to be affected by several factors, including social demography and history of treatment for HIV-infected individuals. These insights can give information for the more effective development and implementation of RDT strategies in response to hard-to-reach or high-risk populations in Indonesia.

## Methods

### *Study design*

This study used a case-control study design and was conducted in 2022. A total of 262 anonymous plasma was obtained in the Institute of Tropical Disease. Two hundred sixty-two individuals, including 131 HIV-infected individuals as the case group and healthy volunteers (recruited from laboratory staff and university students) as the control group, were enrolled in this study. The inclusion criteria in the HIV infected group were adults and confirmed HIV positive by 3 methods and confirmed positive by PCR on one of the gag/env/protease/reverse transcriptase genes. The plasma of HIV patients was used for HIV antibody and antigen detection in this study. The plasma was separated previously from the whole blood and stored at -80°C. Metadata consists of clinical symptoms and patient identities were confirmed by medical records. The inclusion criteria in the healthy volunteers were adults, no HIV infection and willingness to be taken blood samples. Data on variables studied in healthy

volunteers were obtained through a questionnaire. Written informed consent was agreed and signed by each individual prior to sample collection.

*Serological tests for HIV antibody and antigen*

All of plasma of HIV patients and healthy volunteers were analyzed using HIV antibodies rapid tests and antigen ELISA kit. Qualitatively measurement of HIV antibodies using commercial RDT method namely HIV ½ Ab 3-line, Indonesia. While HIV-1 antigen was determined using HIV-1 p24 Elisa assay (XpressBio, USA). All serological tests were performed according to the manufactured instruction's kits.

*Data collection, variables and analysis*

The data collected included the characteristics of the subjects, antibody and antigen detection, also risk factors of positive results of rapid antibody and ELISA antigen tests. The characteristic of subjects was collected such as sex (male or female), age (< 30 years or ≥ 30 years), marital status (married or single/not married yet), HIV patients from medical records and healthy volunteers from questionnaire. Antibody and antigen results by Rapid test and ELISA assay, respectively, were collected by examination in the HIV Laboratory, Institute of Tropical Disease, Universitas Airlangga. The results of antibody test are categorized into reactive and non-reactive by rapid tests. Whereas, the antigen analysis test results were categorized into positive and negative by ELISA assay. The risk factor variables from the reactivity of the antibody and positivity of ELISA test results are the use of anti-retroviral viral (ARV), duration of ARV and HIV transmission variables. ARV use is categorized as drug-treated or drug naïve. The duration of ARV use is presented in months. Transmission of HIV transmission is categorized into non-sexual transmission (IDU and mother to child), and sexual (sexual intercourse, homo, bisexual). Data were analyzed descriptively to see the characteristics of the respondents (This data is shown in Table 1). Bivariable analysis was performed using the chi-square test and Fisher's exact test. Fisher's exact is used when the chi-square test requirements are not met. Data were analyzed using SPSS software.

**Results**

The results showed that all subjects included in the study with characteristics almost the same distribution of gender, age, and marital status (shown in Table 1). In the HIV patient group, more than half of the subjects were male (59.5%), aged ≥ 30 years (78.6%), and married status (67.2%). While, in the control group, more than half of the subjects were female (74%), aged <30 years (64.1%), and single (68.7%). The results of the chi-square analysis showed that sex, age, marital and status were significantly related to HIV status. Men were 4.2 times more likely to be HIV positive than women (OR=4.2, 95% CI=2.49-7.07, p<0.001). Age under 30 years has 85% lower odds of having positive HIV status compared to age ≥ 30 years (OR=0.15, 95% CI=0.09-0.26, p<0.001). Respondents who were single had 78% lower odds of having positive HIV status compared to respondents who were married (OR=0.22, 95% CI=0.13-0.37, p<0.001). Particularly for HIV-infected people, they were sexually infected (55.7%), were received antiretroviral drug treatment (79.4%) and were treated mostly with less than 3 months (84%).

In our study, HIV patients and healthy volunteers were screened for HIV infection using HIV antibodies and antigens as qualitative tests as shown in Figure 1. Rapid test found HIV antibody reactivity in nearly all HIV patients, 97.7% (128/131), but not in healthy volunteers. Only 25.2% (33/131) of HIV patients remained antigen-positive and 3.1% (4/131) of the healthy volunteers were positive for the antigen. The sensitivity and specificity of the two methods are shown in Table 2. The rapid antibody test was more sensitive than the ELISA antigen test (97.7% vs 25.2%) compared to the gold standard for HIV detection using PCR. Also, the specificity of both tests was high (100% vs 96.9%). However, the PPV, NPV, and accuracy of rapid antibody tests were higher than ELISA antigen tests.

The results of the statistical analysis in Table 3 showed that the variables sex, age and marital status of HIV patients were not significantly related to positive results of antibody and antigen tests. Meanwhile, the variable of transmission ways of virus, use of ARVs and duration of ARV had a significant

**Table 1.** The characteristics of subjects involved in this study between HIV patients and healthy volunteers

| Characteristics | | All | | Cases (HIV patients) | | Control (Healthy Volunteer) | | *p*-value | OR | 95%CI | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | n | % | | | Lower | Upper |
| **Sex** | | | | | | | | | | | |
| | Male | 112 | 42.7 | 78 | 59.5 | 34 | 26 | **<0.001** | 4.2 | 2.49 | 7.09 |
| | Female | 150 | 57.3 | 53 | 40.5 | 97 | 74 | | | | |
| **Age** | | | | | | | | | | | |
| | <30 years old | 112 | 42.7 | 28 | 21.4 | 84 | 64.1 | **<0.001** | 0.15 | 0.09 | 0.26 |
| | ≥30 years old | 150 | 57.3 | 103 | 78.6 | 47 | 35.9 | | | | |
| **Marital status** | | | | | | | | | | | |
| | Single | 133 | 50.8 | 43 | 32.8 | 90 | 68.7 | **<0.001** | 0.22 | 0.13 | 0.37 |
| | Married | 129 | 49.2 | 88 | 67.2 | 41 | 31.3 | | | | |
| **Transmission** | Sexual | 73 | 55.7 | 73 | 55.7 | - | - | - | - | - | - |
| | Non-sexual | 58 | 44.3 | 58 | 44.3 | - | - | - | - | - | - |
| **ARV** | Drug Treated | 104 | 79.4 | 104 | 79.4 | - | - | - | - | - | - |
| | Drug Naive | 27 | 20.6 | 27 | 20.6 | - | - | - | - | - | - |
| **Duration of ARV for Patients with Drug Treated** | ≤3 months | 110 | 84 | 110 | 84 | - | - | - | - | - | - |
| | >3 months | 21 | 16 | 21 | 16 | - | - | - | - | - | - |

*Abbreviations:* CI: confidence interval; OR: odds ratio. *p*-value < 0.05 is considered significant difference (value in bold) and was estimated using Chi-square test.

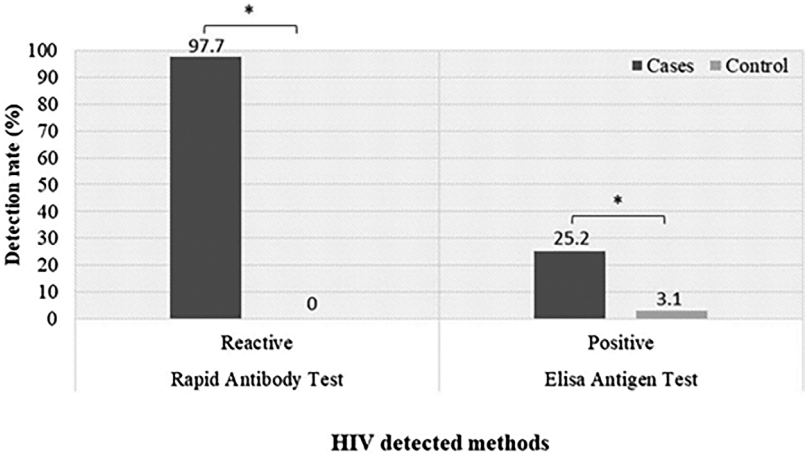


**Figure 1.** Detection rate of HIV Antibody and Antigen screening between HIV patients and Healthy volunteers.

**Table 2.** The sensitivity and specificity of Rapid Antibody and ELISA Antigen tests

| | Rapid Antibody Test | | ELISA Antigen Test | |
|---|---|---|---|---|
| **Reactions** | **Cases (n)** | **Control (n)** | **Cases (n)** | **Control (n)** |
| **Positive** | 128 | 0 | 33 | 4 |
| **Negative** | 3 | 131 | 98 | 127 |
| **Sensitivity (%)** | 97.7 | | 25.2 | |
| **Specificity (%)** | 100 | | 96.9 | |
| **PPV (%)** | 100 | | 89.2 | |
| **NPV (%)** | 97.8 | | 56.4 | |
| **Accuracy (%)** | 98.9 | | 61.1 | |

relationship with the results of the ELISA Antigen test ($p$-value <0.05). Respondents who were likely to be infected through sexual contact were 4.03 times more likely to have reactive antigen ELISA results than non-sexual (OR=4.03, 95%CI=1.6-10.15, $p$-value=0.004). All positive antigen were drug-treated HIV-infected people and undergoing treatment in less than 3 months. All drug-treated HIV patients for more than 3 months were negative antigen (Table 3). Table 4 showed that the results of Rapid Antibody and ELISA Antigen Tests in HIV patients might be affected by the duration of ARV treatments. For the antibody test, most of HIV patients with reactive results had an average duration of ARV was longer than non-reactive (2.94 vs 2.00 months). In contrast, HIV patients with positive antigen by ELISA had a shorter mean duration of ARV therapy (2.12 months), compared with a mean duration of 3.29 months for negative results.

## Discussion

Indonesia has the second highest number of people living with HIV (PLWH) in the South East Asia Region (SEAR) and the infection rate has increased significantly every year from 5,846 in 2004 to 242.699 in 2017 (15). Despite a 19% decline in new HIV infections between 2014 and 2017, the risk of HIV transmission remains high (16). High-risk populations often have limited access to relevant HIV education and social services due to a lack of knowledge and HIV stigma. This, in turn, could lead to underserved healthcare and underreporting of HIV in more remote areas of the country (15,17,18). Hence, the level of HIV knowledge is a key factor for HIV prevention and a risk factor for early detection (19). HIV screening in early detection is important to reduce HIV transmission and of course to increase patient awareness to start antiretroviral treatment. In 2014, the Centers for Disease Control and Prevention (CDC) issued new guidance for HIV diagnostic testing, which included primary testing by a combination immunoassay that detects both HIV-1 and HIV-2 antibodies and the HIV-1 p24 antigen. Specimens reactive by the screening assay undergo supplemental testing with an immunoassay that differentiates HIV-1 and HIV-2 antibodies (20). Specimens that are reactive on initial antigen/antibody combination immunoassays and nonreactive or indeterminate in the HIV-1/HIV-2 antibody differentiation immunoassay are then tested with an FDA-approved HIV-1 RNA nucleic acid test (NAT) (20). In the study, we detected HIV-antigen and antibody among Indonesians in comparing between HIV patients and healthy volunteers. Our findings showed that in the HIV patient group, more than half of the subjects were male (59.5%), aged ≥30 years (78.6%), and married status (67.2%) compared to healthy volunteers. HIV prevalence among women is also rising year by year, accounting for 32% of all people living with HIV in 2017 (16,21). The analysis of HIV case surveillance clearly shows that there are significant differences and levels in the ratio of male to female in Indonesia. Area of Indonesia where most of the population lives, more men are being infected than women with an F/M ratio of 0.7 whereas in Papua the ratio is the opposite with more women infected than

**Table 3.** HIV-patients characteristics based on results of Rapid Antibody and ELISA Antigen Tests

| Characteristics | | HIV Antibody | | | | | | | | HIV Antigen | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Reactive | | Non-reactive | | | | 95%CI | | Positive | | Negative | | | | 95%CI | |
| | | n | % | n | % | *p*-value | OR | Lower | Upper | n | % | n | % | *p*-value | OR | Lower | Upper |
| **Sex** | Male | 75 | 58.6 | 3 | 100 | 0.396 | NA | NA | NA | 17 | 51.5 | 61 | 62.6 | 0.378 | 0.64 | 0.29 | 1.43 |
| | Female | 53 | 41.4 | 0 | 0 | | | | | 16 | 48.5 | 37 | 37.8 | | | | |
| | Total | 128 | 100 | 3 | 100 | | | | | 33 | 100 | 98 | 100 | | | | |
| **Age** | <30 years old | 27 | 21.1 | 1 | 33.3 | 0.517 | 0.54 | 0.05 | 6.12 | 9 | 27.3 | 19 | 19.4 | 0.478 | 1.56 | 0.62 | 3.89 |
| | ≥30 years old | 101 | 78.9 | 2 | 66.7 | | | | | 24 | 72.7 | 79 | 80.6 | | | | |
| | Total | 128 | 100 | 3 | 100 | | | | | 33 | 100 | 98 | 100 | | | | |
| **Marital status** | Single | 42 | 32.8 | 1 | 33.3 | 1 | 0.98 | 0.09 | 1.06 | 12 | 36.4 | 31 | 31.6 | 0.775 | 1.24 | 0.54 | 2.82 |
| | Married | 86 | 67.2 | 2 | 66.7 | | | | | 21 | 63.6 | 67 | 68.4 | | | | |
| | Total | 128 | 100 | 3 | 100 | | | | | 33 | 100 | 98 | 100 | | | | |
| **Transmission** | Sexual | 71 | 55.5 | 2 | 66.7 | 1 | 0.62 | 0.06 | 7.04 | 26 | 78.8 | 47 | 48 | **0.004** | 4.03 | 1.6 | 10.15 |
| | Non-sexual | 57 | 44.5 | 1 | 33.3 | | | | | 7 | 21.2 | 51 | 52 | | | | |
| | Total | 128 | 100 | 3 | 100 | | | | | 33 | 100 | 98 | 100 | | | | |
| **ARV** | Drug Treated | 102 | 79.7 | 2 | 66.7 | 0.503 | 1.96 | 0.17 | 22.48 | 33 | 100 | 71 | 72.4 | **0.002** | NA | NA | NA |
| | Drug Naïve | 26 | 20.3 | 1 | 33.3 | | | | | 0 | 0 | 27 | 27.6 | | | | |
| | Total | 128 | 100 | 3 | 100 | | | | | 33 | 100 | 98 | 100 | | | | |
| **ARV time in patients treated** | ≤3 months | 81 | 79.4 | 2 | 100 | 1 | NA | NA | NA | 33 | 100 | 50 | 70.4 | **0.000** | NA | NA | NA |
| | >3 months | 21 | 20.6 | 0 | 0 | | | | | 0 | 0 | 21 | 29.6 | | | | |
| | Total | 102 | 100 | 2 | 100 | | | | | 33 | 100 | 71 | 100 | | | | |

*Abbreviations:* CI: confidence interval; OR: odds ratio. *p*-value < 0.05 is considered significant difference (value in bold) and was estimated using Chi-square test.

**Table 4.** The correlation of duration of ARV treatments with the results of Rapid Antibody and ELISA Antigen Tests in HIV patients

| Duration of ART | N (%) | Mean (months) | Std. Deviation | Std. Error Mean | *p*-value |
|---|---|---|---|---|---|
| **Rapid Antibody Test** | | | | | |
| **Reactive** | 102 (98.1) | 2.94 | 2.01 | 0.20 | 0.513 |
| **Non-reactive** | 2 (1.9) | 2.00 | 0.00 | 0.00 | |
| **ELISA Antigen Test** | | | | | |
| **Positive** | 33 (31.7) | 2.12 | 0.65 | 0.11 | **<0.001** |
| **Negative** | 71 (68.3) | 3.29 | 2.28 | 0.27 | |

*p*-value < 0.05 is considered significant difference (value in bold) and was estimated using t test.

men and the ratio is 1.3 F/M. More men than women are living with HIV because epidemics may be concentrated among men who have sex with men, people who inject drugs, sex workers and their male clients (22,23). Most reported HIV infections are men, but nearly 60% of reported HIV cases in Papua are women, compared to 37% in the rest of the country (24). Importantly, women have higher biological susceptibility to HIV and STIs than men because of a larger surface area of mucous membrane being exposed during sexual intercourse and because of hormonal suppression of the immune system in the female genital tract during the secretory stage of the menstrual cycle (23,25). Our study found that men had slightly higher rates of HIV infection than women. According to the US Centers for Disease Control and Prevention, from 2001 to 2014, the percentage of people living with HIV who are 50 or older increased by more than 100%, and more than half of those living with HIV are older than 50 (26). The proportion of PLHIV50+ has increased significantly from 8% in 2000 to 16% in 2016 and is expected to increase to 21% by 2020. In 2016, 80% of people living with HIV50+ lived in low- and middle-income countries (LMICs), with the highest number of people living in Eastern and Southern Africa. While high-income countries have a higher proportion of PLHIV50+, low- and middle-income countries have a higher number of PLHIV50+ that is expected to continue to increase by 2020 (27) Analysis of national survey data shows people over 50 are more than twice as likely to have HIV comorbidities than people under 50. The findings that older people living with HIV have higher rates of chronic disease compared with younger people living with HIV in South Africa (28). In Indonesia, the Ministry of Health reported 377.564 cases in 2019 and 86.5 percent of the cases are the productive ages (29). This report is similar to our findings that the age of HIV patients ≥30 years is higher. The HIV cases in our study were mainly married persons. Sexual intercourse is the major mode of HIV transmission, resulting in more antigens being detected in the sexual group than in the non-sexual group. Indeed, married couples are particularly vulnerable to HIV infection and transmission. Partners who have unprotected sex outside their partners or who are in the acute phase of a new infection present a significant risk of further transmission within the partner. Without help, these HIV-positive individuals in a relationship will likely spread the virus to their partners (30–32). Apart from extramarital sex, HIV can also be spread through the sharing of toothbrushes, razor blades, needles, and other personal items. Therefore, it is important to prevent HIV transmission, and married couples should maintain mutual fidelity in marriage. HIV antibodies detected by the rapid test in our study were found mainly in HIV patients but none in healthy volunteers. Moreover, age, sex marital status, ARV, duration of treatment and route of transmission was not related to antibody positivity. Our study shows that HIV antibodies can be used as a predictor of infection among healthy people. ARV-treated and untreated subjects mostly developed antibodies. Maturation of the antibody response against the HIV reservoir at the time of ART initiation might be important implications for HIV remission studies showing that autologous IgG antibodies

block the outgrowth of a substantial but variable fraction of viruses in the latent reservoir for HIV-1 (33). Qualitative detection of antigens by ELISA can be used to assess HIV infection. In our study, not all HIV patients were antigen positive, only 25%. In addition, approximately 3.1% of healthy volunteers tested positive for HIV antigens but were not positive for the virus by PCR. This result suggested that there may be false positives in ELISA antigen detection. ELISA is highly sensitive, which makes it useful for early detection, but this sensitivity can lead to false-positive results, especially in low-prevalence populations or healthy individuals (like blood donors or volunteers). Among blood donors screened with 4th-generation ELISA tests, a small percentage had reactive results that were not confirmed by Western blot or PCR, indicating false positives (34,35). Antiretroviral therapy increases HIV-specific immune responses, decreases levels of viral antigens (36,37). Nevertheless, HIV antibody and T-cell response may be induced and sustained by the intermittent antigen expression. The immune response continues to sense HIV-infected cells in people with ARV (37). Although ARVs are not a cure for HIV infection, ARVs can reduce plasma HIV RNA levels in HIV-positive individuals to below the detection limit of commercial assays and may contribute to the reduction of HIV antigen detection (38). But the reservoir of HIV latent still present. Previous study showed that cell latently infected with HIV DNA do not express antigen and make them invisible to the immune system (39). In our study, there were significant differences in ARV, duration of treatment, and route of transmission between HIV antigen-positive and negative groups. Prolonged treatment may affect antigen reduction. Antigen-positive patients were found in HIV patients who received antiretroviral therapy for less than 3 months and none with more than 3 months. Treatment-naïve patients and some patients who received the drug for less than 3 months did not show antigen positivity, suggesting that they may have a good immune response or we need to check the viral load of HIV. The rapid antibody test used in the study was more sensitive and specific than the antigen test using ELISA, when compared to the gold standard PCR test. We suggested that rapid antibody test may be used as screening and diagnosis for HIV infection in the population, especially in high-prevalence area. Meanwhile, antigen testing can be used to monitor the success of treatment. However, HIV infection has so far no cure for the disease, but we can control the prognosis of the disease. HIV testing may be the only way to detect the virus and possibly prevent its spread to others. Likewise, people living with HIV who are taking antiretroviral therapy and who are virally suppressed do not transmit HIV to their sexual partners. Limitations of the study are the sample size and variables of antiretroviral drug use and duration of treatment that require further study for antigen testing.

## Conclusion

Data demography of gender, age, and marital status might be risk factors for HIV infection. Circulating HIV antibodies, predominantly present in HIV-infected individuals, may be better predictors of current HIV infection, more practical and critical than HIV antigens as a population screen in Indonesia.

**Ethic Approval:** This study was approved by the Institutional Ethics Committees of Airlangga University (approval number:189/HRECC.FODM/IV/2022).

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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**Correspondence:**
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Siti Qamariyah Khairunisa
Institute of Tropical Disease, Universitas Airlangga,
Jl Mulyorejo UNAIR Kampus C, 60115, Surabaya, Indonesia.
E-mail: skhairunisa@staf.unair.ac.id
ORCID: 0000-0002-0006-4229