

A systematic review and meta-analysis of HIV transmission risk behaviors, genetic variations, and antiretroviral (ARV) resistance in LGBT populations

Journal of Public Health Research
2024, Vol. 13(2), 1–11
© The Author(s) 2024
DOI: 10.1177/22799036241239464
journals.sagepub.com/home/phj



Dewi Ratna Sulistina^{1,2}, Santi Martini³, Budi Prasetyo⁴,
Firman Suryadi Rahman⁵ , Arga Setyo Adji⁶, Chung-Yi Li⁷
and Maria Inge Lusida^{8,9}

Abstract

Background: Currently, human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) has become one of the major health problems worldwide, including Indonesia. East Java is one of the provinces in Indonesia with the highest prevalence of HIV infection. One of the causes of HIV infection transmission is lesbian, gay, bisexual, and transgender (LGBT) practice. Furthermore, the treatment using antiretroviral (ARV) drugs in HIV-I patients can fail due to the presence of HIV drug resistance.

Objective: The aim of this study is to identify the behavior at risk of HIV transmission among LGBT, patterns of genetic variation and antiretroviral (ARV) resistance.

Methods: A systematic review and meta-analysis based on the PRISMA guidelines was conducted. We searched three databases including PubMed, ScienceDirect, and Google scholar for studies investigating the non-heterosexual behavior as risk factor of HIV infection and antiretroviral resistance. Only studies published in English are considered. The adjusted estimates of the risk were carried out using best-adjusted OR with 95% confidence interval (CI) and significant p value < 0.05 .

Results: In the quantitative analysis of HIV infection risk factors, a total of 13 studies were included, which investigated non-heterosexual behavior as a potential factor. The studies involved a total of 37,129 participants, comprising 10,449 individuals in the non-heterosexual behavior group (LGBTQ+) and 26,680 individuals in the heterosexual group. The majority of the participants in this study were from the USA, Japan, China, and Brazil, and the main HIV subgenotypes were B and CRF. Additionally, the antiretroviral resistance of HIV patients was examined, involving a total of 3062 individuals, with 1296 individuals in the non-heterosexual behavior group and 1766 individuals in the heterosexual group. Our calculation showed that non-heterosexual behavior was significant as risk factor of HIV infection (OR = 2.17, 95% CI = 1.94–2.43, $p < 0.001$) and antiretroviral resistance (OR = 1.31, 95% CI = 1.00–1.71, $p = 0.05$).

¹Doctoral Study Program, Faculty of Public Health, Universitas Airlangga, Surabaya, East Java, Indonesia

²Department of Sport Science, Faculty of Sport Science, State University of Malang, Malang, Indonesia

³Division of Epidemiology, Faculty of Public Health, Universitas Airlangga, Surabaya, East Java, Indonesia

⁴Department of Social Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

⁵Faculty of Public Health, Universitas Airlangga, Surabaya, East Java, Indonesia

⁶Faculty of Medicine, Hang Tuah University, Surabaya, East Java, Indonesia

⁷Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

⁸Department of Microbiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

⁹Institute of Tropical Disease, Universitas Airlangga, Surabaya, Indonesia

Corresponding author:

Santi Martini, Division of Epidemiology, Faculty of Public Health, Universitas Airlangga, Kampus C Unair, Surabaya, East Java 60111, Indonesia.

Email: santi-m@fkm.unair.ac.id



Conclusion: This study concludes that non heterosexual behavior is significant risk factor of HIV infection. A quite prevalent of antiretroviral resistance were found among non heterosexual behavior. The main subgenotype of HIV are B and CRF.

Keywords

LGBTQ, antiretroviral (ARV) resistance, behavior

Date received: 6 October 2022; accepted: 28 February 2024

Introduction

HIV/AIDS is a global problem in the world. More than 39 million people worldwide die from HIV/AIDS and more than 36 million people live with HIV. HIV infection and AIDS are caused by HIV.¹ There are two types of HIV virus, namely HIV type 1 (HIV-1) and HIV type 2 (HIV-2). HIV disease in the world is generally caused by HIV-1, while HIV-2 is found to be endemic in West Africa.² HIV-1 virus is divided into four groups, namely; M (major), O (outlying), N (new or non-M, non-O) and P (putative). Most HIV-1 infections in America, Europe, and Australia are from group M,³ which is divided into several subtypes, namely: (A [A1, A2, A3,A4], B, C, D, F [F1, F2], G, H, J, and K), as well as about 98 circulating recombinant forms (CRFs) and several unique recombinant forms (URFs) were found in group M. The number of people living with HIV in the world is also known to increase by 2 million people per year.⁴

Based on global data, HIV/AIDS remains a major health problem worldwide. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), approximately 38.4 million people were living with HIV in 2021.⁵ Despite significant progress in reducing the number of new infections, HIV continues to spread at an alarming rate in certain regions, particularly in sub-Saharan Africa.⁶ In addition to sexual transmission, HIV can also be transmitted through blood transfusions, sharing of needles among intravenous drug users, and from mother to child during pregnancy, childbirth, or breastfeeding.⁷ The high prevalence of HIV/AIDS in certain regions is often linked to factors such as poverty, lack of education, and limited access to healthcare services⁸ Stigma and discrimination against people living with HIV can also contribute to the spread of the disease by discouraging individuals from seeking testing and treatment.

In Indonesia, HIV/AIDS is a significant health issue, with around 630,000 (540.000–740.000) people living with HIV. While the incidence of HIV infection in Southeast Asia is declining, it is increasing in Indonesia⁹ The province of West Java has the highest number of cases, followed by DKI Jakarta, East Java, and Papua¹⁰ East Java has one of the highest HIV infection rates, especially in the city of Surabaya, where there is a high

population rate, numerous entertainment venues, and unsafe sex practices. The spread of HIV in the city of Surabaya is fast due to the fast population rate, lots of entertainment venues, and unsafe sex. There was an increase in the incidence of HIV in Surabaya from 501 in 2013, to 572 in 2014.¹¹ Furthermore, in 2018, 1.588 new cases of HIV and AIDS were found in Surabaya.^{12,13} The attraction to the same sex since the age of 15 has been identified as a contributing factor to the transmission of HIV infection. The Ministry of Health has reported that Surabaya, a city in East Java, has one of the highest HIV cases among the gay and transgender population, specifically 3936 gay individuals and 272 transgender individuals with HIV infections.¹³ Furthermore, data in 2021–2022 was also reported that 1155 gay people are infected with HIV. Previous research also stated that the city of Surabaya at risk of having the highest HIV and AIDS cases was Sawahan sub-district, because it was found a group that behaved as gay or male sex men.¹¹ This group is at increased risk of HIV, due to unsafe sex behavior by not using condoms.¹⁴

Efforts to combat the HIV/AIDS epidemic have focused on a combination of prevention, treatment, and care strategies. Prevention measures include promoting safe sex practices, increasing access to testing and counseling services, and implementing harm reduction programs for intravenous drug users.¹⁵ Treatment options for HIV/AIDS have expanded significantly in recent years, with antiretroviral therapy (ART) proving highly effective at reducing the progression of the disease and improving quality of life for those living with HIV. While progress has been made in addressing the HIV/AIDS epidemic, it remains a significant global health challenge that requires ongoing attention and investment. Governments, international organizations, and civil society groups must continue to work together to promote prevention, increase access to testing and treatment, and reduce stigma and discrimination against people living with HIV/AIDS.¹⁶

Factors that cause at-risk groups such as LGBT people to engage in unsafe sex are not wearing condoms, besides, they are influenced by social, environmental and structural factors based on socioecological. This model is a model to predict the behavior of both individual, social,

environmental and policy levels. Structural factors consist of discrimination against the LGBT community and the lack of policies regarding the use of condoms. Environmental factors consist of not being able to access and unavailability of condoms as well as limited health service providers and also the cost of access to health services. The social indicator is the absence of social capital to access condoms and the individual factor is low self-efficacy.¹⁴ Model socioecological contains cognitive factors, especially knowledge.¹⁷ These factors influence LGBT to prevent risky behavior, especially unsafe sex behavior, there by increasing the prevalence of HIV incidence.

Previous studies also reported that mortality and morbidity rate related to HIV could also decreased by antiretroviral therapy (ART). Biophysical and biochemical observations on the development of antiretroviral drugs used for HIV treatment were carried out in vitro using the B subtype and most of the data on the genetic mechanism of drug resistance were from the B subtype. Even so, the drug developed can still be used in patients with other HIV subtypes. The first line of treatment for HIV is a combination of zidovudine (AZT), lamivudine (3TC), and nevirapine (NVP). AZT and NVP can be replaced by stavudine (d4T) and efavirenz (EFV) respectively.¹⁸ Treatment using antiretroviral drugs in HIV-1 patients can fail due to the presence of HIV drug resistance (HIVDR).^{19–21}

This is in accordance with a previous study entitled “Prevalence of HIV Infection and Resistance Mutations in Patients Hospitalized for Febrile Illness in Indonesia.” The results of the analysis on 39 HIV cases with HIV RNA levels 100, sequencing examinations for genotyping analysis and resistance testing were successfully carried out in 30 (77%) subjects. Five (17%) subjects had resistance mutations. The five subjects identified resistance mutations to nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). There is no evidence of drug resistance being transmitted to the 15 newly diagnosed HIV patients. Fifteen adults and two child subjects with HIV died. Overall mortality was 37% (17/46) among people living with HIV (PLHIV) subjects, compared with 5% (70/1406) among the non-HIV group (p 0.01) 3 months after hospitalization. The mortality rate for patients with previously diagnosed HIV and patients with previously unknown HIV status was similar (32.4% vs 33%).²² With the emergence of the problem of resistance to antiretroviral drugs (ARVs) in Indonesia, it will increase the failure of HIV/AIDS therapy. People living with HIV/AIDS (PLWHA) will be more susceptible to severe, deadly infections, so that the morbidity and mortality of HIV/AIDS will increase. Based on the above background, the purpose of this study was to identify the sexual behavior of HIV infection at risk of lesbian, gay, bisexual, and transgender (LGBT), patterns of genetic variation and antiretroviral (ARV) resistance.

Methods

Data search

Searching protocol was carried out using several databases, such as PubMed, ScienceDirect, and Google Scholar for articles up through the last February 2022. The formula search employed Boolean “AND” or “OR” with “homosexual,” “human immunodeficiency virus,” “HIV,” “antiretroviral resistance,” “lesbian,” “men sex men,” “transgender,” “non heterosexual behavior,” and “risk” keywords.

Selection criteria

Studies included must meet the following criteria such as: (1) The result reported association of non heterosexual behavior and HIV patients; (2) the research calculated the number of population into categories based on two variables (non heterosexual behavior and HIV status); (3) cross-sectional, cohort, and case-control study design; and (4) English-language studies. The study selection, quality evaluation, and data extraction were all done independently by three reviewers. The issue between the three reviewers was settled by consensus among the fourth reviewers. This study was designed using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline guidelines.

Outcome definition

The major outcomes of this study including non heterosexual behavior as risk factor of HIV infection; and HIV patient with non heterosexual behavior with antiretroviral resistance in the form of odd ratio (OR; 95% CI). First, the reviewers retrieved the baseline characteristics, exposures, and outcomes of included studies independently including name of authors, publication year, design of research, the country location, study periods (yr), and the number of people that participated (HIV positive and total population) were all collected.

We also assess the quality outcome of the included study using Modified Newcastle Ottawa Scale (NOS) which has three components: Patient selection (five points), group comparability (two point), and exposure determination (three points). Measurement in the selection components includes: Proper case definition, case representativeness, control group selection, and definition. Measurement in the comparability components includes: Research controls for the most and extra factor. Measurement in the exposure domain includes: Exposure determination, method of cases and controls determination, and rate of non-response. The overall score varied from 0 (worst) to 10 (best). the overall quality was rated as good quality (3 or 4 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/

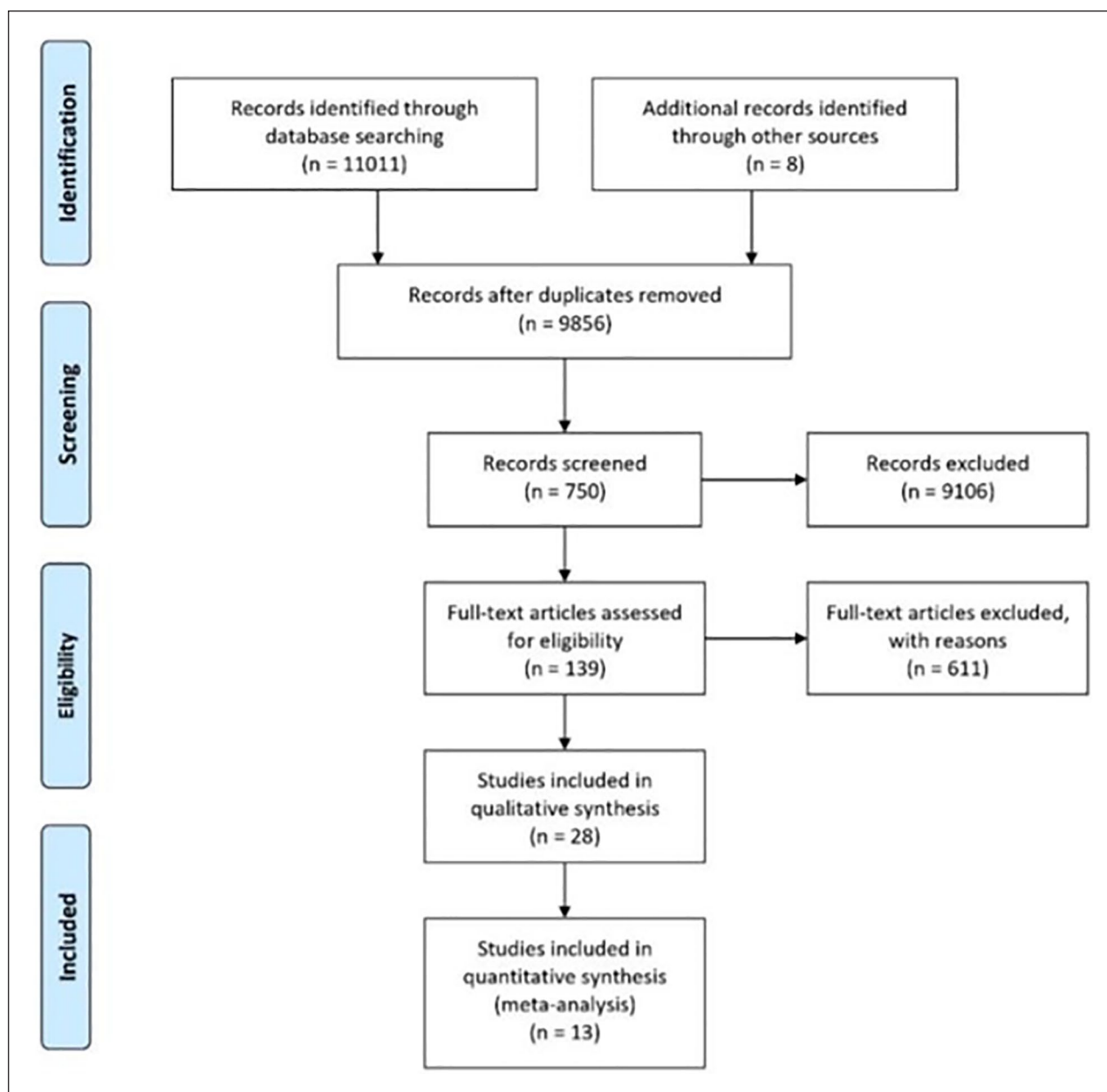


Figure 1. PRISMA flowchart.

exposure domain); fair quality (2 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain), and poor quality (0 or 1 star in selection domain or 0 stars in comparability domain or 0 or 1 stars in outcome/exposure domain).

Data analysis

The adjusted estimates of the risk were carried out using best-adjusted OR with 95% confidence interval (CI) and significant p value < 0.05 . The Q -test was used to measure heterogeneity with a significance set at $p < 0.05$.

Result

Search result

In the study search process, we collected 11,018 studies with 11,011 originating from online databases (PubMed, ScienceDirect, and Google scholar) and 8 study originating from data sources previously identified by the authors. A total of 9856 studies were obtained after removing duplicates using computer software (Citation Manager). In the title and abstract screening process, 139 studies were obtained that could be assessed for eligibility (eligibility). Furthermore, 111 studies were

Table 1. Data characteristics.

No.	Author, year	Study design	Study periods	Location (country)	Population		Therapy/treatment for HIV patient
					HIV positive*	Total	
1	Andersson, 2018	Cohort	2010–2016	Swedia	1713	1713	NRTI, NNRTI, PI
2	Biagetti, 2009	Cohort	2006–2007	Italy	81	81	NRTI, NNRTI, PI
3	Burrel, 2010	Cross sectional	2008	South Africa	56	537	ART
4	Cardoso, 2009	Cross sectional	2007–2008	Brazil	97	97	NRTI, NNRTI, PI
5	Chen, 2018	Cross sectional	2014	China	291	2828	N.A.
6	Chen, 2020	Cohort	2016–2018	Taiwan	462	462	NRTI, NNRTI, PI, STR, InSTI
7	DiazGranados, 2010	Cross sectional	N.A	Colombia	180	180	NRTI, NNRTI, PI
8	Flentje, 2017	Cohort	2008–2010	San Fransisco	252	300	N.A.
9	Gatanaga, 2007	Cross sectional	2003–2004	Japan	575	575	NRTI, NNRTI, PI
10	Hattori, 2010	Cohort	2003–2008	Japan	2573	2573	NRTI, NNRTI, PI
11	Huaman, 2011	Cohort	2006–2008	USA	133	133	NRTI, NNRTI, PI
12	Kojima, 2013	Cohort	2006–2011	Japan	133	266	N.A
13	Kumar, 2020	Cross sectional	2014–2015	India	786	23,081	N.A.
14	Murillo, 2010	Cohort	2004–2007	Honduras	200	200	NRTI, NNRTI, PI
15	Nebhinani, 2011	Cross sectional	N.A	India	100	140	Not given
16	Palma, 2007	Cross sectional	2003	Portugal	180	180	NRTI, NNRTI, PI
17	Pando, 2011	Cross sectional	2006–2008	Argentina	273	12,192	NRTI, NNRTI, PI
18	Politch, 2012	Cohort	N.A	USA	18	101	PI
19	Ristig, 2002	Cohort	1996–2001	USA	62	75	NRTI, NNRTI, PI
20	Sabino, 1996	Cross sectional	1993	Brazil	80	80	N.A.
21	Sanchez-Gomez, 2014	Cross sectional	2010–2011	Ekuador	50	369	ART
22	Sayan, 2013	Cohort	2009–2012	Turkey	117	117	NRTI, NNRTI, PI
23	Siegel, 2010	Cohort	2004–2007	USA	59	59	ART
24	Skoura, 2012	Cohort	2009–2011	Northern Greece	238	238	NRTI, NNRTI
25	Tanaka, 2019	Cross sectional	2011–2014	Brazil	150	190	NRTI, NNRTI, PI
26	Wensing, 2008	Cross sectional	2002–2003	16 European countries and Israel	1050	1050	NRTI, NNRTI, PI
27	Zhang, 2013	Cross sectional	2011	China	44	463	N.A.
28	Zheng, 2020	Cross sectional	2018	China	83	1330	ART

*HIV positive population across studies globally.

excluded cause by unmatched with the inclusion and exclusion criteria which resulting as qualitative analysis using 28 included studies (systematic study) and quantitative analysis (meta-analysis) using 13 included studies. The entire literature search process follows the PRISMA Guideline and is summarized through a flow-chart as follows (Figure 1)

Outcomes of studies

Data characteristics of all studies that meet the inclusion criteria are compiled in Table 1. All of the included studies are observational studies written in English. The study periods range from 1 to 7 years. Total participants were 49,610 with 10,036 are HIV positive. The major study outcomes were described in Table 2.

A total of 13 studies were included in the quantitative analysis of non heterosexual behavior as risk factor of HIV infection using a total of 37,129 people including 10,449 in the non heterosexual behavior (LGBTQ+) group and

26,680 in the heterosexual group. In other hand, the analysis of HIV patient with non heterosexual behavior as risk factor of antiretroviral resistance using a total of 3062 people including 1296 in the non heterosexual behavior (LGBTQ+) group and 1766 in the heterosexual group. The risk levels were assessed using the odd ratio (OR) approach using fixed model analysis. Our calculation showed (Figure 2) that non heterosexual behavior as risk factor of HIV infection was significant different in overall analysis (OR=2.17, 95% CI=1.94–2.43, $p < 0.001$). Our calculation also showed (Figure 3) that non heterosexual behavior as risk factor of antiretroviral resistance was significant different in overall analysis (OR=1.31, 95% CI=1.00–1.71, $p = 0.05$).

Heterogeneity

Q-Test was used to evaluate evidence of heterogeneity. Our analysis showed that non heterosexual behavior (LGBTQ+) as risk factor of HIV infection ($p < 0.001$)

Table 2. Study outcomes.

No.	Author, year	Genetic subtype	Main result	NOS component		Quality of study	
				Selection	Comparability		
1	Andersson, 2018	B, A, C, CRF_01A_E, CRF_02A_G	TDR was found in 7.1% of the population. TDR for NNRTIs grew dramatically from 1.5% in 2010 to 6.2% in 2016 and was linked to infection and/or origin in Sub-Saharan Africa (SSA). An MSM transmission cluster with the M41L SDRM from the 1990s was discovered. TDR to tenofovir (TDF) ($n=8$), emtricitabine/lamivudine ($n=9$), or both ($n=8$) was observed in 25 (1.5%) individuals.	4	1	2	Good
2	Biagetti, 2009	B, A1, CRF01_A_E, CRF02_A_G	All of the patients with resistance mutations belonged to the Caucasian, Italian, or subtype B groups. Males had a higher incidence of resistance than females, and homosexuals had a higher frequency of resistance than heterosexuals.	3	1	2	Good
3	Burrell, 2010	N.A.	Self-identifying as gay, homosexual or queer (adjusted odds ratio (AOR) 4.5, 95% confidence interval (CI) 1.0–20.0) and reporting ever having had a sexually transmissible infection diagnosis (AOR 4.3, 95% CI: 2.3–8.3) were significantly predictive of testing HIV-1 positive, while reporting unprotected anal intercourse with a known HIV-negative partner (AOR 0.4, 95% CI: 0.2–0.9) was significantly protective.	4	2	2	Good
4	Cardoso, 2009	B, C, F1, Mosaic	Primary drug resistance mutations ranged from 8% (IAS) to 10% (SDRM). High level resistance to at least one antiretroviral drug was observed. T215D/S revertant mutations were identified in 4/97 patients. HIV-1 subtype B represented 82.5%, subtype F1 6.2%, subtype C 3.1%, B/F1 7.2% and one sample was a F1/C/B mosaic. HIV-1 subtype C sequences formed a monophyletic cluster with other Brazilian subtype C sequences	5	2	3	Good
5	Chen, 2018	CRF08_B_C, URF, CRF01_A_E, CRF07_B_C, C, CRF55_01B, B, CRF64_B_C	CRF08 BC, URFs, CRF01_AE, and CRF07_BC remained the most common strains. CRF01_AE, CRF07_BC, and CRF08 BC EPSs remained steady at a high level. Yunnan maintained a low rate of transferred HIV-1 drug resistance.	3	2	3	Good
6	Chen, 2020	N.A.	A total of 462 participants were enrolled, included 384 recreational drug users and 78 non-recreational drug users. Methamphetamine and nitrites were two most common recreational drugs. Recreational drug use was significantly associated with STDs in one-year follow-up period but was not significantly associated with unreported viral load.	5	1	3	Good
7	DiazGranados, 2010	N.A.	One hundred and three naive and 77 experienced patients were included. Resistance mutations were found in 66 patients (65.7%) with failure. The most common mutations were 184V, 103 N, G190A/S, and L90 M.	5	2	3	Good
8	Flehtje, 2017	N.A.	Among 300 women, 24% reported nonheterosexual identity at the first study visit. Consistent with minority stress theory, lesbian and bisexual identity were associated with higher levels of mental health comorbidity, and bisexual identity was related to greater rates of substance use disorders and mood disorders.	4	1	3	Good
9	Gatanaga, 2007	B, non-B	Twenty-three cases, including three recently infected patients, were infected with HIV-1 having major drug-resistance mutations, including M41L, D67N, L100I, K103N, V106A, M184I, M184V, L210W, and revertant mutations at the 215 codon in reverse transcriptase and M46I in protease encoding regions.	5	2	2	Good
10	Hattori, 2010	B, non-B (AE, C, AG, A, G, F, D), other	In the 6-year study period, the prevalence of drug-resistant HIV-1 among 2573 patients, consisting mainly of Japanese men in their late-30s and infected through male-to-male sexual contacts, followed an increasing trend from 5.9% (16/273) in 2003 to 8.3% (50/605) in 2008. Nucleoside reverse transcriptase inhibitor associated mutations predominated in each year, with T215 revertants being the most abundant. The predictive factor for drug-resistant HIV-1 transmission was subtype B, and those for recent HIV-1 infection were male gender, MSM behavior, Japanese nationality, and subtype B.	4	1	3	Good
11	Huaman, 2011	N.A.	The prevalence of TDRM was 17% (23/133). Non-nucleoside reverse transcriptase mutations occurred in 11 (8%), nucleoside reverse transcriptase mutations in 13 (10%), and protease inhibitor mutations in 10 (8%).	4	1	3	Good
12	Kojima, 2013	B, CRF01_A_E, C	There was no statistically significant link between HIV and <i>Treponema pallidum</i> infection. The different HBV genotypes Ae and G were found in the HIV-positive population.	4	1	3	Good
13	Kumar, 2020	N.A.	Significantly higher HIV prevalence (3.8%, $p < 0.05$) was reported among MR-MSM, despite 97.2% of them being aware of HIV.	3	2	3	Good
14	Murillo, 2010	B, non-B	Among 200 samples analyzed from Honduran patients the prevalence of TDR was 7% (95% CI: 3.9–11.5), 5% for non-nucleoside reverse transcriptase inhibitors (NNRTIs), 3% for nucleoside reverse transcriptase inhibitors (NRTIs) and 0.5% for protease inhibitors (PIs).	4	1	2	Good

(Continued)

Table 2. (Continued)

No.	Author, year	Genetic subtype	Main result	NOS component			Quality of study
				Selection	Comparability	Outcome	
15	Nebhinani, 2011	N.A.	The HIV group reported sexual contact as the commonest source of infection (58%) and had a lower prevalence of psychiatric disorders (45% vs 60%), as compared to the rheumatoid arthritis group.	4	2	3	Good
16	Palma, 2007	A, B, C, G, U, H	The most common route of transmission was heterosexual contact (54.4%), followed by intravenous drug use (20%), homo/bisexual individuals (19.4%) and blood transfusion (0.6%). The commonest subtypes were B (41.7%) and G (29.4%), while other non-B subtypes rated 12.8% and recombinant forms represented 16.1% of the samples. Fourteen patients (7.78%) were identified as carrying resistance-associated mutations.	5	2	3	Good
17	Pando, 2011	B, BF, C	HIV prevalence was shown to be greater among trans SWs, male SWs, and MSM. MSM and male SWs had the highest prevalence of subtype B, whereas female DUs, female SWs, and PW had the highest prevalence of intersubtype BF recombinant.	4	1	1	Fair
18	Politch, 2012	N.A.	A significant frequency of seminal HIV shedding in a group of HIV-infected MSM on HAART who are sexually active HIV in sperm was linked to HIV detection in blood, as well as STIs and genital irritation in males who were totally suppressed.	3	1	1	Poor
19	Ristig, 2002	N.A.	Resistance was found in 11% of the population. Between 1996 and 1998, a frequency of 4% was found. During the succeeding decade of 1999 to 2001, the incidence rose to 17%.	3	1	2	Good
20	Sabino, 1996	F, B	Subtype F is associated with drug injection in Brazil.	4	1	2	Good
21	Sanchez-Gomez, 2014	A, B, other	HIV infection was associated with age 25 or older, active syphilis and homosexual self-identification.	5	2	3	Good
22	Sayan, 2013	B, CRF 02_AG, F1, CRF 01_AE, CRF 12_BF, CRF 03_AB, G, C, D, A1	The most prevalent HIV-1 subtypes in Turkey were CRFs (CRF 02_AG, CRF 01_AE, CRF 12_BF, and CRF 03_AB, NNRTI, and PI).	4	1	3	Good
23	Siegel, 2010	N.A.	Results showed differences between the heterosexual women and the gay and bisexual men. Most of the young women were asymptomatic when they tested positive. Many young men were experiencing symptoms of illness when they tested positive, and about half of them recognized their symptoms as related to HIV and sought tests.	4	1	3	Good
24	Skoura, 2012	A, B, other	Transmitted drug resistance was documented in 21.8% of patients enrolled, affecting approximately 40% of subtype A HIV-1-infected individuals	4	1	3	Good
25	Tanaka, 2019	B, F1, C	There are no associations between sexual orientation and the existence of transmitted drug resistance mutations (TDRM).	4	2	2	Good
26	Wensing, 2008	B	The total incidence of viruses containing drug-resistance mutations was 9.1%. The majority had only one amino acid alteration, which had no influence on projected drug susceptibility. Resistance to NRTI was seen most commonly, followed by resistance to protease inhibitors and resistance to NNRTIs.	5	2	3	Good
27	Zhang, 2013	N.A.	age (> 35 years old), cohabitation, more than 10 years of homosexual behavior and more than 10 homosexual partners were risk factors which associated with the HIV infection, and that protected sex during the past 6 months was a protective factor for the HIV infection.	4	1	3	Good
28	Zheng, 2020	CRF07_B C	Risk factors including having 2–5 same sex partners (aOR 2.43, 95% CI 1.28–4.64), always (aOR 5.93, 95% CI 1.59–22.13) or sometimes (aOR 4.25, 95% CI 2.09–8.64) having unprotected anal intercourse, taking both, insertive and receptive sex roles (aOR 4.95, 95% CI 2.57–9.53) or only the receptive sex role (aOR 2.26, 95% CI 1.21–4.24) positively associated with HIV infection.	5	2	3	Good

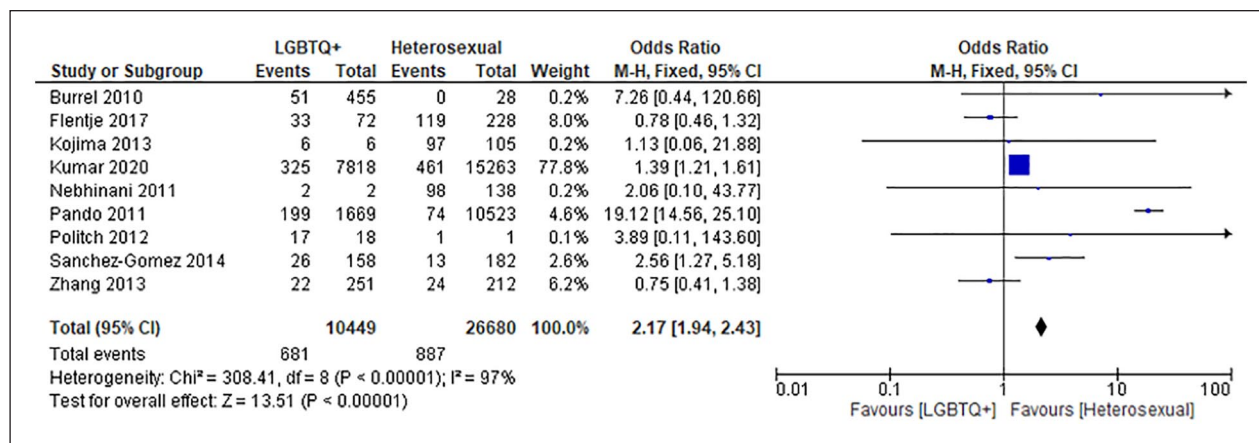


Figure 2. Non heterosexual behavior (LGBTQ+) as risk factor of HIV infection.

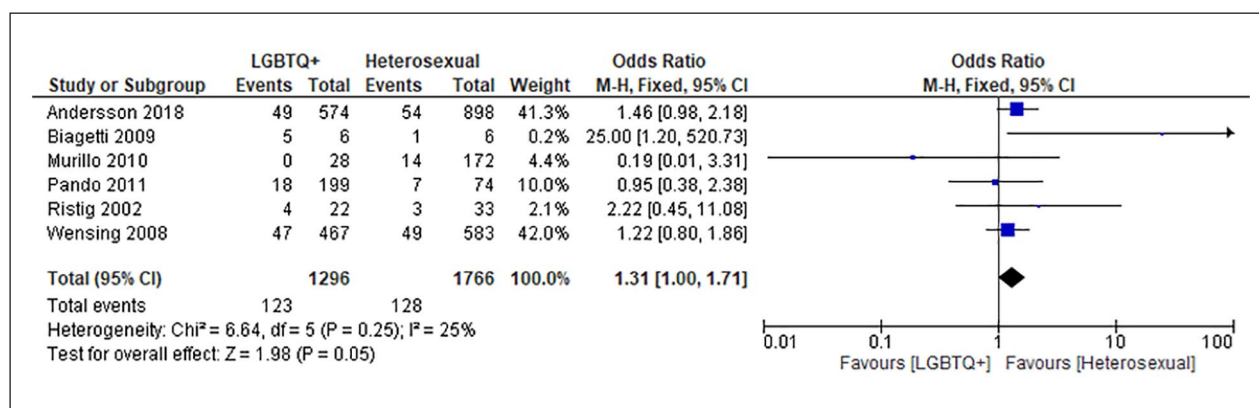


Figure 3. Non heterosexual behavior (LGBTQ+) as risk factor of antiretroviral resistance.

was found to have no heterogeneity which was also supported by the I^2 test value < 50%. In other hand, non heterosexual behavior (LGBTQ+) as risk factor of antiretroviral resistance ($p=0.05$) was found to have heterogeneity which was also supported by the I^2 test value > 50%.

Discussion

Our study shows that non heterosexual behavior is a risk factor for HIV infection. A previous study by Skoura et al. stated that several risk factors for HIV infection are men who have sex with men, heterosexual behavior, and injecting drug users.²³ These results are also supported by a study conducted by Champion and Szlachta on 93 men who have had sexual relations with men or women. Fifty-four people from the study were LGBT and 39 were heterosexual. The behaviors studied in this study included condom use, anal sex, oral sex with men, group sex, sex with men and women, sex with prostitutes, sex in bathhouse, use of sex toys, drug use, and sharing needles are associated with the incidence of HIV infection.²⁴

Other studies have also shown that sexual orientation may be associated with HIV risk behaviors, especially in those who have sex with men and also have sex with women.²⁵ The use of condoms and antiretroviral (ART) has been associated with a significant reduction in the risk of sexually transmitted HIV, in both homosexuals and heterosexuals. Better risk reduction can be achieved by combining condom use and ART.^{26,27} Consistent condom use was found to lead to a better reduction in the risk of transmitting HIV infection.²⁸ The risk of disease transmission was also found to be lower in vaginal sex compared to anal sex.²⁹ Another study of male-male relationships stated that receptive anal sex had a higher risk of transmission than insertive anal sex, however, the risk of transmission was also observed to be increased in women who had anal sex or in heterosexual intercourse.³⁰ Early ART use was found to have a lower risk of disease transmission when compared to delayed treatment. The risk of disease transmission was also found to be lower on ART than without ART.³¹

HIV-1 exhibits substantial genetic variation as a result of various factors, including the reverse transcriptase (RT)

lack of proofreading capabilities, the fast turnover of HIV-1 in vivo, host selection immunological forces, and recombination events during replication. Because of this variation, HIV-1 variations are divided into three primary phylogenetic groups: M (main), O (outlier), and N (non-M/non-O). Initially, HIV-1 subtypes were classified based on the subgenomic regions of particular genes. The most common HIV-1 genetic forms in worldwide are subtypes A, B, and C, with subtype C accounting for over half of all HIV-1 infections. The ability of lymphoid cells located in vaginal and rectal tissues to transmit and replicate information is an essential future concern.³² HIV-1 circulating strains in blood donors were predicted to help to comprehensive AIDS control and the establishment of appropriate HIV-1 diagnoses in China.³³

Subtype B is prominent in Europe, the Americas, and Oceania. Meanwhile, subtype CRF01_AE is prevalent in Asia and CRF02_AG is prevalent in Western Africa. The dynamic shift in HIV subtype distribution poses new problems for HIV diagnosis, treatment, and vaccine design-development in the future. The increased prevalence of recombinant viruses shows that coinfection and superinfection by divergent HIV strains has grown increasingly widespread, needing continual monitoring to track viral variety. Approaches to near full-length genome sequencing that are less expensive are crucial for improving HIV subtype estimates. However, missing subtype data and poor sequence sampling levels continue to be a problem in several geographical areas.³⁴

According to a Surabaya research, the majority of integrase genes were identified as CRF01_AE genes, and 40% of them contained an uncommon insertion in the integrase C-terminus.³⁵ Most HIV-positive female commercial sex workers in Surabaya have HIV-1 CRF01_AE viral gene fragments. The main reason is that they were unaware of sexually transmitted illnesses and had unprotected intercourse with their clients.³⁶ Similar like Surabaya, an investigation in North Sulawaesi showed CRF01_AE gene is the major subtype of HIV-1 infection.³⁰ The major subtypes prevalent in another study in Papua and West Papua provinces are also CRF01_AE and subtype B.³¹ Previous study in Kepulauan Riau found that the most prevalent HIV-1 subtype was CRF01_AE, recombinant between CRF01_AE and subtype B, and subtype B.³

Drug resistance mutation is the major cause of antiretroviral medication failure, making AIDS treatment difficult. Drug resistance in HIV-1 is produced by mutations in the RT and protease enzymes, which are the molecular targets of antiretroviral treatment. With the emergence of HIV-1 medication resistance mutations, the initial antiretroviral treatments are unable to suppress the resistant virus, and the viral load may skyrocket. Drug resistance mutations to NRTIs and NNRTIs were complicated and common, and were the

most common cause of first-line antiretroviral treatment failure. The prevalence of medication resistance mutations varied considerably amongst individuals according on their age, infection route, treatment duration, initial antiretroviral regimen, and viral load.³⁷

Our study indicates LGBT may be one of the antiretroviral resistant. Transgender people are a disenfranchised population of people with low adherence to HIV therapy, and as a result, they are more prone to acquire resistance. There is also evidence that HIV positive transgender sex workers use condoms less than males who have sex with men, implying that men who have sex with transgender are more likely to get HIV.³⁸ In Guangdong Province, drug resistance mutations were more common in NNRTIs among MSM with ART failure. A complicated transmission pattern was identified by transmission network analysis, and greater attention should be paid to younger HIV-1-infected MSM with many linkages.³⁹ Another evaluation of ARV effect in Bali reported that the patients who undergo more than 12 months of NRTIs treatment show a decrease in the mtDNA:nDNA ratios.³⁶ Study in Surabaya showed that transmitted drug resistance of RT inhibitors was detected in 4.3% of the samples.³

A study in Papua showed high prevalence of HIV-1 patient because health behavior that associated with social culture.³⁷ Another investigation in Papua showed the best predictor of viral suppression at 12 and 36 months is virological response 6 months after starting ART, which may aid in identifying individuals who require extra adherence treatment assistance. Patients' immunological results are influenced favorably by higher baseline CD4 levels.³⁸ HBV infection was related with age over 25, receptive anal intercourse, MSM past sex with women, and a history of sexually transmitted illnesses (STIs).³⁹ Another study in Sorong, West Papua reported that mutations for the RT inhibitors, A62V and E138A appeared in a few samples, indicating the possible emergence of transmitted HIV-1 drug resistance.³² Another study of HIV-1-infected patients in Surabaya reported that major drug resistance mutations found in the RT genes, predominantly M184V, K103N, and thymidine analog mutations (TAMs).⁴⁰ Major mutations including M184V and Y188L were found in participant of previous study in Kepulauan Riau.³²

Conclusion

This study concludes that non heterosexual behavior is significant risk factor of HIV infection. This study also found that there was a quite prevalent of antiretroviral resistance among non heterosexual behavior. The main subgenotype of HIV are B and CRF. Preventive measures through education and outreach should be implemented so as to prevent the transmission of HIV infection.


Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Firman Suryadi Rahman  <https://orcid.org/0000-0002-1245-4400>

References

- Kapila A, Chaudhary S, Sharma RB, et al. A review on: HIV AIDS. *Indian J Pharm Biol Res* 2016; 4(03): 69–73.
- Nyamweya S, Hegedus A, Jaye A, et al. Comparing HIV-1 and HIV-2 infection: Lessons for viral immunopathogenesis. *Rev Med Virol* 2013; 23(4): 221–240.
- Kotaki T, Khairunisa SQ, Witaningrum AM, et al. HIV-1 transmitted drug resistance mutations among antiretroviral therapy-Naïve individuals in Surabaya, Indonesia. *AIDS Res Ther* 2015; 12(1): 5.
- Pandey A and Galvani AP. The global burden of HIV and prospects for control. *Lancet HIV* 2019; 6(12): e809–e811.
- UNAIDS. The joint United Nations programme on HIV/AIDS (UNAIDS), <https://www.unaids.org/en> (8 May 2021, accessed 8 May 2023).
- Kharsany AB and Karim QA. HIV infection and AIDS in Sub-Saharan Africa: current status, challenges and opportunities. *Open AIDS J* 2016; 10(1): 34–48.
- Waymack JR and Sundareshan V. *Acquired immune deficiency syndrome*. Treasure Island, FL: StatPearls Publishing, 2023.
- Muula AS. HIV infection and AIDS among young women in South Africa. *Croat Med J* 2008; 49(3): 423–435.
- Ibrahim K, Songwathana P, Boonyasopun U, et al. The HIV/AIDS epidemic in Indonesia: does primary health care as a prevention and intervention strategy work? *Int J Nurs Pract* 2010; 16(2): 87–91.
- National AIDS Commission Secretary. *National HIV and AIDS Strategy and Action Plan 2010-2014*. National AIDS Commission Secretary, 2012, p.90.
- Yohanes F. Policy implementation of HIV and AIDS management in the city of Surabaya (Study of regional regulation of the City of Surabaya Number 4 of 2013, case study at the Putat Jaya Health Center, City of Surabaya). *J Penelit Adm Publik* 2015; 1(01): 83–175.
- Huda JM, Joko P and Fitriyah I. Interpersonal communication between PLWHA to grow the motivation back to normal life in Mahameru Foundation Surabaya. *J Komun Prof* 2019; 3(1): 12–22.
- Kemenkes RI. Infodatin HIV AIDS. *Kementerian Kesehatan Republik Indonesia*, <https://pusdatin.kemkes.go.id/resources/download/pusdatin/infodatin/infodatin-2020-HIV.pdf> (2020, accessed 9 May 2023).
- Restar A, Ogunbajo A, Adia A, et al. Using structural equation modelling to characterise multilevel socioecological predictors and mediators of condom use among transgender women and cisgender men who have sex with men in the Philippines. *BMJ Glob Health* 2020; 5(7): DOI: 10.1136/bmjgh-2020-002463: e002463.
- Volkow ND and Montaner J. The urgency of providing comprehensive and integrated treatment for substance abusers with HIV. *Health Aff* 2011; 30(8): 1411–1419.
- Bekker LG, Alleyne G, Baral S, et al. Advancing global health and strengthening the HIV response in the era of the sustainable development goals: the International AIDS Society—Lancet Commission. *Lancet* 2018; 392(10144): 312–358.
- Bronfenbrenner U and Morris PA. *The ecology of developmental processes*. 5th ed. Hoboken, NJ: John Wiley & Sons Inc, 1998. Vol. 1.
- Espada JP, Morales A, Guillén-Riquelme A, et al. Predicting condom use in adolescents: a test of three socio-cognitive models using a structural equation modeling approach. *BMC Public Health* 2016; 16(1): 35.
- Tsimbos C and Verropoulou G. Demographic and socioeconomic determinants of low birth weight and preterm births among natives and immigrants in Greece: an analysis using nationwide vital registration micro-data. *J Biosoc Sci* 2011; 43(3): 271–283.
- Sungkanuparph S, Sukasem C, Kiertiburanakul S, et al. Emergence of HIV-1 drug resistance mutations among antiretroviral-naïve HIV-1-infected patients after rapid scaling up of antiretroviral therapy in Thailand. *J Int AIDS Soc* 2012; 15(1): 12–12.
- Merati TP, Karyana M, Tjitra E, et al. Prevalence of HIV infection and resistance mutations in patients hospitalized for febrile illness in Indonesia. *Am J Trop Med Hyg* 2021; 105(4): 960–965.
- Sungkanuparph S, Oyomopito R, Sirivichayakul S, et al. 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. *Clin Infect Dis* 2011; 52(8): 1053–1057.
- Skoura L, Metallidis S, Pilalas D, et al. High rates of transmitted drug resistance among newly-diagnosed antiretroviral naïve HIV patients in northern Greece, data from 2009-2011. *Clin Microbiol Infect* 2013; 19(3): E169–E172.
- Champion JD and Szlachta A. Self-identified sexual orientation and sexual risk behavior among HIV-infected Latino males. *J Assoc Nurses AIDS Care* 2016; 27(5): 585–594.
- Mutchler MG, Bogart LM, Elliott MN, et al. Psychosocial correlates of unprotected sex without disclosure of HIV-positivity among African-American, Latino, and white men who have sex with men and women. *Arch Sex Behav* 2008; 37(5): 736–747.
- LeMessurier J, Traversy G, Varsaneux O, et al. Risk of sexual transmission of human immunodeficiency virus with antiretroviral therapy, suppressed viral load and condom use: A systematic review. *CMAJ* 2018; 190(46): E1350–E1360.
- Liu H, Su Y, Zhu L, et al. Effectiveness of ART and condom use for prevention of sexual HIV transmission in serodiscordant couples: A systematic review and meta-analysis. *PLoS One* 2014; 9(11): e111175.
- Patel P, Borkowf CB, Brooks JT, et al. Estimating per-act HIV transmission risk: a systematic review. *AIDS* 2014; 28(10): 1509–1519.

29. Baggaley RF, Owen BN, Silhol R, et al. Does per-act HIV-1 transmission risk through anal sex vary by gender? An updated systematic review and meta-analysis. *Am J Reprod Immunol* 2018; 80(5): e13039.
30. Gartner MJ, Roche M, Churchill MJ, et al. Understanding the mechanisms driving the spread of subtype C HIV-1. *EBioMedicine* 2020; 53: DOI: 10.1016/j.ebiom.2020.102682: 1–6.
31. Ueda S, Witaningrum AM, Khairunisa SQ, et al. Genetic diversity and drug resistance of HIV-1 circulating in North Sulawesi, Indonesia. *AIDS Res Hum Retroviruses* 2019; 35(4): 407–413.
32. Khairunisa SQ, Ueda S, Witaningrum AM, et al. Genotypic characterization of human immunodeficiency virus type 1 prevalent in Kepulauan Riau, Indonesia. *AIDS Res Hum Retroviruses* 2018; 34(6): 555–560.
33. Luo XL, Mo LD, Su GS, et al. Incidence and types of HIV-1 drug resistance mutation among patients failing first-line antiretroviral therapy. *J Pharmacol Sci* 2019; 139(4): 275–279.
34. Gorbach PM, Javanbakht M, Bornfleth L, et al. Drug resistant HIV: behaviors and characteristics among Los Angeles men who have sex with men with new HIV diagnosis. *PLoS One* 2017; 12(3): e0173892.
35. Lan Y, Deng X, Li L, et al. Hiv-1 drug resistance and genetic transmission networks among MSM failing antiretroviral therapy in South China 2014-2019. *Infect Drug Resist* 2021; 14: 2977–2989.
36. Masyeni S, Sintya E, Megawati D, et al. Evaluation of antiretroviral effect on mitochondrial DNA depletion among HIV-infected patients in Bali. *HIV/AIDS Res Palliat Care* 2018; 10: 145–150.
37. Kayame R and Thaha R. Proactive approaches in HIV/AIDS based on local culture, the Mee tribe in central mountains of Papua, Indonesia. *Int J Sci Res Publ* 2014; 4(5): 1–9.
38. Limmade Y, Fransisca L, Rodriguez-Fernandez R, et al. HIV treatment outcomes following antiretroviral therapy initiation and monitoring: a workplace program in Papua, Indonesia. *PLoS One* 2019; 14(2): e0212432.
39. Oliveira MP, Matos MAD, Silva ÁMC, et al. Prevalence, risk behaviors, and virological characteristics of Hepatitis B virus infection in a group of men who have sex with men in Brazil: results from a respondent-driven sampling survey. *PLoS One* 2016; 11(8): e0160916.
40. Khairunisa SQ, Kotaki T, Witaningrum AM, et al. Appearance of drug resistance-associated mutations in human immunodeficiency virus type 1 protease and reverse transcriptase derived from drug-treated Indonesian patients. *AIDS Res Hum Retroviruses* 2015; 31(2): 255–259.