

PUBLIKASI ILMIAH

**MORTALITY RATE OF PEOPLE LIVING WITH HIV/AIDS ON INJECTION DRUG
USERS (IDU) COMPARED TO NON-INJECTION DRUG USERS (NON-IDU)**

Diajukan sebagai syarat meraih gelar sarjana pada Fakultas Kedokteran
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ABSTRACT

Risk factors for transmission of HIV/AIDS are heterosexual (84.7%), Injection Drugs User (IDU) (5.7%), homosexual (4.7%), perinatal transmission (4.6%) and blood transfusion (0.1%). As the second-largest risk factor, IDU is a serious public health concern because of its high potential in transmitting HIV. The transmission of HIV in the IDU group with the unhygienic use of syringes is mostly related to hepatitis infection. On the other hand, the transmission of HIV in non-IDU is due to substance abuse, inconsistent condom use, sex work, and promiscuity. The aim of this review is to differentiate the mortality rates on IDU and non-IDU. Our search strategy was carried out by looking through scientific articles published from 2010 to 2021 from PubMed, Google Scholar, and non-peer-reviewed literature. We obtained 25 articles, but only 7 articles are considered relevant. Our findings indicate that the IDU group has a 50% higher mortality rate than non-IDU due to HIV-related complications and co-morbidities such as Hepatitis C. The comparison of survival between IDU and non-IDU for IDU is 53.2% [95% CI: 48.1-58.3], and non-IDU is 82,1% (95% CI: 80.7-83.6) respectively. Indeed, at the time of HIV diagnosis, higher CD4+ counts were present in the IDU group (IDU: median 358 cells/ml, IQR (200–561 cells/ml); non-IDU: median 300 cells/ml, IQR (130–486 cells/ml; P=0.0003). Therefore, our finding suggests that mortality rate in the IDU group is relatively higher compared to non-IDU.

Keywords: HIV/AIDS, transmission, mortality, injection, drug user, IDU, non-IDU.

1. INTRODUCTION

Human Immunodeficiency Virus or in another word is HIV has a meaning of a virus that infects the immune system of the body and make a person more susceptible to infections and any other diseases. HIV infection originally occurred from a kind of chimpanzee in Central Africa and then spread to humans. Slowly, HIV spread throughout Africa and then to the whole world over the decades. In the United States, HIV began to spread since the mid to late 1970s [1].

HIV infection or Acquired Immune Deficiency Syndrome (AIDS) began to be known since 1983, until the end of 2007 HIV infection affected about 33.2 million people in the world and caused around 2.1 million deaths. Day by day beyond 6,800 people are infected with HIV and 5,700 people die because of

AIDS, which means one person dies every 15 seconds [2]. In 2007 more than 2.5 million new cases of HIV infection occurred, this figure was up 15% from 2001, when the United Nations Program on Acquired Immune Deficiency Syndrome (UNAIDS) announced that HIV infected 29 million people in the world with 1.7 million deaths [2].

The most risk factors for HIV/AIDS transmission until 2015 occurred in heterosexuals (84.7%), Injection Drugs Users (IDU) (5.7%), homosexuals (4.7%), perinatal transmission (4.6%) and blood transfusion (0.1%) (Marlinda & Azinar, 2017). Among these factors, the PLWHA group with Injection Drug User (IDU) had a higher mortality rate than the group with other triggering factors [3]. Although direct injection drug use only accounts for 5% -10% of worldwide

Human Immunodeficiency Virus (HIV) infections, the mortality rate has increased to 30%. This is because the death of AIDS patients in the IDU group was caused by co-morbidities or comorbidities. In the PLWHA group of IDUs with the use of non-sterile injecting equipment, hepatitis C contamination will occur, so that HIV patients with co-infection with HCV contribute to the increasing cause of death in IDUs with AIDS. Furthermore, IDU's are often prevented from getting health services and even decide to stop their treatment so that it can make the situation worse. This is because HIV/AIDS is still considered as a taboo disease even in the family and health services so that patients can't open up to them and increasingly feel they do not have a comfortable place [4]. Another factor that contributes to the increase in HIV infection is the lack of public knowledge about HIV/AIDS and its transmission, so that PLWHA and their families are vulnerable to stigma and discrimination which result in barriers to obtaining care and treatment [4]. The non-IDU PLWHA group also showed an increase in prevalence worldwide, which was around 3.7% in Mexico and 16.0% in the United States. The cause of the increase in prevalence in the Non-IDU group caused by the use of polysubstances, inconsistent condom, commercial sex work, and multiple partners [5].

Seeing the increasing mortality rate in PLWHA IDU groups, the authors are interested in exploring the factors that influence mortality rates in PLWHA IDU and non-IDU groups. It is hoped that by conducting a literature review, the authors can find out the factors that affect the comparison of the mortality rate of PLWHA in the IDU and Non IDU groups.

2. METHOD

We conducted a national and international literature search using the PubMed, Google Scholar, and non-peer-reviewed databases. There is no manual hand search for this literature review. At the stage of the initial search articles journal, obtained 25 articles in the span of time in 2010 to 2021 by using keywords HIV [Ti] AND transmission AND (Injection [Ti] OR "Drugs injection") AND (Mortality [Tiab] OR "Death Case"). From the number of these, only around 10 journals that are *free access* and considered relevant. This published research article containing information and data that the authors need related to clinical characteristics such as HIV, IDU, and mortality rates in PLWHA who are IDUs and non-IDUs will be included in this literature review, and exclusion criteria related to acute or chronic illnesses that may limit the ability of patients to

participate in the study and any exposing that could bias the result (HAART).

Two review authors independently assessed the risk of bias in each included study for key criteria: people and outcomes, incomplete outcome data, selective outcome reporting, and other sources of bias. Low risk, high risk, or uncertainty (uncertainty about lack of information or possible bias) was used. The authors settled controversy by consensus.

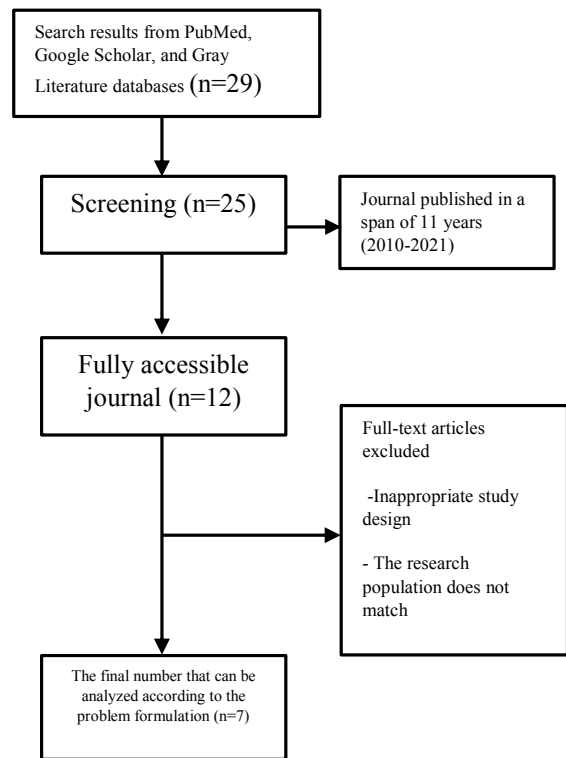


Figure 1. PRISMA flowchart of the studies selection process

3. RESULTS

To find articles, the author conducts a search using the keywords that have been compiled. In the time span between 2010 and 2021, 25 articles were obtained. After selecting inclusion and exclusion criteria, 7 papers were received which would then be analyzed. Each of the 7 journals was selected for careful reading of the abstract, objective, and analytical data from the original study questions to gather information on the comparison of PLWHA's mortality between IDUs and non-IDUs. Of 7 articles selected for this review, 5 from PubMed, 1 from Google Scholar, and 1 from non-peer-reviewed literature, all correspond to quantitative studies. Studies were conducted on various continents, such as Europe and Asia.

Table 1. Comparative data

No	Author	Country	Purpose	Result	Conclusion
1.	Mette V. Larsen, Lars H. Omland, Jan Gerstoft, Carsten S. Larsen, Janne Jensen, Niels Obel & Gitte Kronborg	Denmark, 2010	Investigating the mortality impact of PLWHA who are IDUs and their comparison with non-IDUs	Data from the studied patients showed that 484 (10.6%) were categorized as IDUs and 4094 (89.4%) as non-IDUs. The estimated 10-year survival probability was 53.2% [95% CI: 48.1–58.3] in IDUs and 82.1% (95% CI: 80.7–83.6) in non-IDUs. HIV infection in IDUs more than tripled the cause of death (MRR: 3.2; 95% CI: 2.7-3.8).	The risk of death in people living with HIV who are IDUs increases due to comorbid hepatitis C Virus (HCV) factors and the risk of death is higher than non-IDU
2.	May, Margaret T; Justice, Amy C.; Birnie, Kate; Ingle, Suzanne M; Smith, Colette; Neau, Didier; Guiguet, Marguerite; Schwarze-Zander, Carolynne; Moreno, Santiago; Guest, Jodie L.; Monforte, Antonella d'Arminio; Tural, Cristina; Gill, MichaelJ.; Bregenzer, Andrea; Kirk,	North America and Europe, 2015	Knowing IDU and Hepatitis C as the risk of death in PLWHA compared to non-IDU	Of the 32,703 patients 3,374 (10%) were IDUs; 4,630 (14%) HCV+; 1,116 (3.4%) died. Mortality was higher in IDUs compared to non-IDUs (HR 2.71; 95% CI 2.32, 3.16) and in HCV+ compared with HCV- (2.65; 2.31, 3.04).	Mortality was higher in IDUs compared to non-IDUs and most of the mortality was increased due to HCV. coinfection

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Table 2. Theoretical study data

No.	Author	Country	Purpose	Conclusion	Source
1.	Rafael Alves Guimarães, Roselma Lucchese, Inaina Lara Fernandes, Ivânia Vera, Aurélio Goulart Rodovalho, Vanessa Alves Guimarães, Graciele Cristina Silva, Rodrigo Lopes de Felipe, Paulo Alexandre de Castro, and Priscilla Martins Ferreira	Brazil, 2017	Knowing several risk behaviour of non-IDU for acquiring HIV.	The several risk behaviour, such as polysubstance use, inconsistent use of condoms, sex work, and multiple sexual partners.	PubMed
2.	Rachmat Sumantri, Iman Supandiman, Ponpon Indjradinata, Andre van der Ven, Reinout van Crevel	Indonesia, 2012	Investigating the probability of death of a person living with HIV based on CD4 cell count	Important risk factors for death on HIV-infected AIDS, i.e. CD4 count	PubMed
3.	<u>Allison M. MCFALL</u> , MHS, <u>Sunil S.</u> <u>SOLOMON</u> , MBBS, MPH, PhD, <u>Greg M.</u> <u>LUCAS</u> , MD, PhD, <u>David D. CELENTANO</u> , MHS, ScD, <u>Aylur K.</u>	Northeast India, 2013	Knowing about the prevalence of HIV and the cause.	Women who inject drugs in Northeast India have a high HIV prevalence which was more than	PubMed

	<p><u>SRIKRISHNAN, BA,</u> <u>Muniratnam S.</u> <u>KUMAR, MD, and</u> <u>Shruti H. MEHTA, MPH,</u> PhD</p>			<p>double their hepatitis C (HCV) prevalence. HIV infection is associated with sexual risk factors while injection-related behaviors appear to drive HCV infection.</p>	
4.	<p>Irfan Ardani, Sri Handayani</p>	<p>Indonesia, 2017</p>	<p>Knowing the impact of stigma on ODHA</p>	<p>An IDU infected with HIV very vulnerable to stigma and discrimination. This affects IDU efforts to seek treatment for HIV infection suffered and treatment for drug addiction.</p>	<p>Google Scholar</p>
5.	<p>CDC</p>	<p>America, 2020</p>	<p>Knowing about HIV/AIDS</p>	<p>HIV (Human Immunodeficiency Virus) is a virus that attacks the body's immune system, making a person more susceptible to infection and other disease</p>	<p>Non-peer-reviewed literature</p>

Of the 7 journals obtained, 2 journals use comparative methodology, while the other 5 journals use theoretical studies based on established literature data. According to a study by Larsen et al in Denmark, namely The Danish HIV Cohort Study in 2010 involving 4578 patients, 484 patients (10.6%) were categorized as IDU group and 4,094 patients (89.4%) were categorized as non-IDU group. IDU. In this study, it was found that the IDU group having a higher CD4+ cell count at diagnosis of HIV than the non-IDU group (IDU: median 358 cells/ml, IQR (200–561 cells/ml); non-IDU: median 300 cells /ml, IQR (130–486 cells/ml); P = 0.0003) but the CD4+ cell nadir was lower in the IDU group. Most of the IDU group, 91.3% have co-infection with Hepatitis C Virus (HCV), while the non-IDU group was only 6.8%. The survival rate had a significant difference between the IDU group of 53.2% [95% confidence interval (CI): 48.1-58.3] and the non-IDU group of around 82.1% (95% CI: 80.7-83.6). The causes of death in these patients were grouped into HIV-related and non-HIV-related, such as deaths from cardiovascular disease as many as 9 people or about 3.5% in the non-IDU group and 4 people or around 1.9% in the IDU group, deaths from cancer as many as 39 people. (7.1%) in the non-IDU group and 6 (2.9%) in the IDU group, and deaths from liver-related disease were 13 (2.4%) in the non-IDU group and 15 (7.3%) in the IDU group. A total of 21 deaths were classified as HIV-related in the IDU group and there were 168 deaths in the non-IDU group. The study found that in the IDU group had an increased risk of death from causes that not related to HIV (MRR 4.6: 95% CI 3.8-5.6) [6].

The May, et al study in North America and Europe in 2015 supported this study by obtaining results from 32,703 patients, of which 3374 (10%) were in the IDU group, 4630 (14%) had hepatitis C infection, and 1116 (3.4%) died. Mortality in IDU was higher than in non-IDU (adjusted HR 2.71; 95% CI 2.32-3.16) and mortality in the hepatitis C-infected group was higher than in the HCV- group (2.65; 2.31-3.04). The effect of death associated with HIV liver-related has a very strong relationship with the IDU and hepatitis C group but after being excluded (adjusted) in the IDU group it has a lower association in causing liver-related HIV death when compared to the group of patients with hepatitis C after the group of patients with IDU was excluded (adjusted). Meanwhile, non-liver-related deaths such as deaths from CNS disorders, lung infections, or violent deaths were more associated with the IDU group than with hepatitis C co-infection [3].

4. DISCUSSION

Injectable drug use (IDU) contributes significantly to the morbidity and mortality of Human

Immunodeficiency Virus (HIV) and AIDS infections, in addition to the use of injection needles in drug users will cause other infections that are pathogenic and can be transmitted into blood through contaminated syringes, the infections for instance Hepatitis C Virus (HCV) [7]. Hepatitis C virus infection is generally found in people with HIV, because it has the same blood-borne transmission route. The United Nations Program on HIV/AIDS (UNAIDS) reports that most HIV infections in Indonesia occur through the use of unsterile injecting equipment so that contamination by hepatitis C infection will occur [2]. Thus, HIV patients co-infected with HCV contributed significantly to the cause of death in the HIV group with IDUs. This is proven and strengthened from the two studies above, namely: Larsen et al. 2010 in Denmark and May, Margaret T, et al. There was a significant difference in mortality between HCV co-infected IDU and non-IDU in North America in 2015, which became evident after adjusting for HCV infection in the HIV-IDU group. IDU and non-IDU. Another fact that the mortality rate in the IDU group with HCV co-infection was higher than in the non-IDU group; We found a higher CD4 cell count in the HIV-IDU group than in the non-IDU group. This is in consistent with a 2010 study by Larsen et al in Denmark, namely data from the Danish HIV Cohort Study (DHCS) which has been approved by the Danish Data Protection Agency.

Table 3. Patients’ characteristic by infection category; n: 4578

Characteristic	IDUs	Non-IDUs	P
Subjects n (%)	484 (10.6)	4094 (89.4)	
Person years of follow up	3187	27216	
CD4+ Cell count (cell/μl) at baseline Median (IQR)	312 (170-544)	280 (130-462)	0.0003
Nadir CD4+ cell count cells (cell/ μl) Median (IQR)	207 (97-387)	238 (120-373)	0.0003
Ever	299 (61.8)	1737 (42.4)	<0.00

Characteristic	IDUs	Non-IDUs	P
diagnosed with HIV before 1 January 1997 n (%)			01
Had exposed by HAART n (%)	345 (71.9)	3248 (79.9)	<0.0001
HCV Positive n (%)	442 (91.3)	280 (6.8)	<0.0001
Negative n (%)	24 (5.0)	3639 (88.9)	
Not tested n (%)	18 (3.7)	175 (4.3)	

IDUs: injecting drug users; IQR: Interquartile range; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HAART: Highly active antiretroviral therapy
Source: Larsen, 2010

As many as 4578 patients, 484 (10.6%) patients in the IDU group and 4094 (89.4%) were categorized as non-IDU groups, where the IDU group had a higher CD4+ cell count at diagnosis of HIV than the non-IDU (IDU: median, 358 cells/ml, IQR (200–561 cells/ml); non-IDU: median 300 cells/ml, IQR (130–486 cells/ml); P = 0.0003) but the nadir number of CD4+ cells in the IDU group was lower, and Around 91.3% in the IDU group were accompanied by co-infected HCV while non-IDU was only 6.8%.

Table 5. Cause of deaths affected person with HIV inflamed via IDU in comparison to non-IDU and sufferers with HCV-inflamed and HCV-uninfected

Cause of death	No. deaths (%)	IDU Versus Non-IDU		HCV-Infected versus HCV-Uninfected	
		HR (95% CI)	Additionally Adjusted for HCV	HR (95% CI)	Additionally Adjusted for IDU
All	1116 (100)	2.71 (2.32 to 3.16)	1.57 (1.27 to 1.94)	2.65 (2.31 to 3.04)	2.04 (1.68 to 2.47)
AIDS	459 (41.1)	1.40 (1.05 to 1.88)	1.01 (0.69 to 1.48)	1.55 (1.21 to 1.99)	1.54 (1.11 to 2.14)
Non-AIDS Infections	84 (7.5)	3.18 (1.89 to 5.34)	1.86 (0.88 to 3.93)	2.92 (1.82 to 4.71)	1.99 (1.00 to 3.99)

Table 4. Mortality rates (MR) in HIV-1 infected through Injectable Drug Use (IDU) versus those infected through other routes

Death Category	Route of infection	Number of deaths	PYR
Overall	Non-IDU	547	2721
	IDU	206	63187
HIV-related	Non-IDU	168	2721
	IDU	21	63187
Not related to HIV	Non-IDU	330	2721
	IDU	166	63187

PYR: Person-years
Source: Larsen, 2010

Based on table 2, 753 (16.5%) patients died. IDU as many as 206 patients (42.3%) and non-IDU as many as 547 (13.4%) [6].

According to research by Larsen et al. in Denmark in 2010 a population-based, countrywide, population-based study of HIV-infected patients found that the overall mortality rate for HIV-positive patients infected by injection was significantly higher than for patients infected by other routes (non-IDU).

This study is supported by other studies, namely a study by May, et al in North America and Europe in 2015 which resulted in 32,703 patients, of whom 3374 (10%) were IDUs, 4630 (14%) had HCV, and 1116 (3.4%) died. The mortality rate of IDU was higher than of non-IDU (adjusted HR 2.71; 95% CI 2.32-3.16) and the hepatitis C-infected group had a higher mortality rate than the non-HCV-infected group (2.65; 2.31-3.04).

Has a relation to liver	69 (6.2)	10.89 (6.47 to 18.3)	2.43 (1.24 to 4.78)	14.0 (8.05 to 24.5)	7.97 (3.83 to 16.6)
Non-AIDS malignancy	103 (9.2)	1.50 (0.78 to 2.88p)	0.72 (0.33 to 1.58)	2.22 (1.38 to 3.58)	2.58 (1.45 to 4.60)

The effect of HIV liver-related mortality was very strongly associated with the IDU group with hepatitis C, but after adjusting for the IDU group there was no significant difference in mortality compared to the HIV-liver related group and group with HCV. Other than liver-related causes such as death from CNS disorders, the presence of lung infection, or the incidence of violent death are more associated with IDU use than with HCV co-infection [3].

5. CONCLUSION

According to our journal review results, risk factors for HIV transmission may be through the IDU group and the non-IDU group, but the HIV transmission rate is higher due to the non-IDU, but the mortality rate is higher in the IDU group than in the non-IDU group, and the IDU group A higher rate of co-infection with hepatitis C in the IDU group was associated with better survival in the non-IDU group.

AUTHORS’ CONTRIBUTIONS

All authors conceived and designed the study. CW and NPWPNP reviewed the literature. NPWPNP, JR, NAP, PWPI, SC, and WAF analyzed the data and wrote the paper. NPWPNP developed the manuscript and all authors contributed to manuscript revision. All authors have read and accepted the final manuscript.

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