Viral Hepatitis-HIV Co-Infection and their associated factors in Negeri Sembilan - a cross sectional study from HIV Case Registry

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Abstract

Background: Viral Hepatitis HIV Co-infection is an important and preventable cause of chronic liver disease, and having them lead to many consequences, especially for those living in wrenched conditions. Thus it is a significant health issue in the communities. This study aimed to determine the prevalence of Viral Hepatitis-HIV Co-Infection and determine the associated variables with this Co-Infection.

Methods: A cross-sectional study was done using HIV Case Registry (Anti Retroviral -(ARV) line listing). We included 1274 patients who were seen under the HIV Clinic services, which were screened for Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) upon registered to the clinic. Factors associated with the HBV-HIV and HCV-HIV were determined using bivariate, and multivariate logistic regression analysis using SPSS and odds ratio was used as the measures of association. A P-value of less than 0.05 was considered statistically significant for all the tests.

Results: From the 1274 number of HIV patients, the prevalence of HBV-HIV is 5.6% (71 cases), while the prevalence with HCV co-infection was 14.8% (189 cases). As for the frequency of multiple HIV-Coinfection, out of 238 HIV cases with Co-Infection, the majority of 167 cases (70.17%) were HCV-HIV Co-Infected followed by 49 cases (20.5%) were HBV-HIV Co-Infected. In comparison, another 22 cases (9.24%) were Co-Infected with HBV-HCV-HIV. In the final model of HBV-HIV Co-Infection, only male gender, CD4 count category less than 199 cells/mm3 and primary care type of facilities were associated with the disease whereas, in the HCV-HIV Coinfection, only male gender, Malay race, Intravenous Drug User (IVDU) modes of transmission, and source of the case from high-risk screening program were associated with the disease**.**

Conclusions: Co-Infection with HCV-HIV is more prevalent from HBV-HIV in our study population. A more targeted intervention of HBV revaccination and more frequent screening of HCV post HCV treatment as reinfection is anticipated in high-risk behaviour patient are some of the intervention programs that can be suggested.

Background Of Study

In Malaysia, the number of cases for HIV has increased dramatically from the first 3 cases in 1986 to 111 196 cases in 2016. The most recent data in 2016 revealed Malaysia country recorded 93 089 people living with HIV (PLHIV) and 18 827 cases for AIDS-related deaths. [1]. However, there is no nationally published data for the prevalence on Viral Hepatitis HIV Co-Infection, available for references but, according to a study in one tertiary hospital in Malaysia, utilizing data from 2007 till 2012, it was discovered that the prevalence of HBV-HIV Co-Infection was 13% while for the HCV-HIV Co-Infection was 18%.[2]

Hepatitis is among five leading infectious diseases that continue to cause significant morbidity and mortality in HIV-infected individuals globally other than Tuberculosis, Cryptococcal Meningitis, [illegible]HCV affects 2.3% of people living with HIV worldwide and up

to 90% of those are linked to people who inject drugs (PWID). On the other hand, HBV infection affects 7.4% of people living with HIV, and this co-infection is frequent, especially within key populations including men who have sex with men (MSM) since HIV and HBV share the same transmission routes (mainly via sexual transmission) [4, 5]. In Southeast Asia, the prevalence of HBV-HIV Co-Infection and HCV -HIV Co-Infection were 10.5 and 15.2% respectively.[6]

There are multiple consequences from HIV-Co Infection amongst the HIV patients, in which having them has led to a more unsatisfactory outcome. HIV-Co Infection leads to health problems and death especially for those living in wrenched condition, causes them to live a lower quality life, reduces their response to antiretroviral treatment also have resulted in an increase of stigma from the public, leading to a limitation for them to work, hence failing to manage higher medical cost [7]. Viral hepatitis is the seventh most common cause of mortality worldwide, and out of all the viral hepatitis-related deaths, approximately 48% are attributable to HBV and HCV.[8] Besides, chronic viral hepatitis also has emerged as the majority and a significant cause of morbidity and mortality among PLHIV [4, 9, 10]

Clinically, the effects of HIV on HBV Disease Progression has led to a lower probability of spontaneous clearance of acute Hepatitis B infection, higher HBV replication, more rapid declination in Hepatitis B surface antibody (anti-HBs), more episodes of reactivation, lower seroconversion rates from HBeAg to anti-HBe antibody. [11, 12].

Meanwhile, for the effect of HIV on HCV patients, it would be difficult to clear HCV viremia and have a higher HCV RNA viral loads. This chain of effects explains why liver disease has become a major cause of death in HIV infection, and 66% are secondary to HCV.[13, 14]. Both HBV and HCV HIV Co-Infection can lead to a higher risk of death and more rapid progression to liver fibrosis and cirrhosis.[14-17]. These complications will incur greater costs for treatment and care. [18]

In Malaysia, the screening program for Hepatitis B and Hepatitis C amongst HIV patients has started in government healthcare facilities since 27 May 1998. [19, 20]. This screening program will be followed by a treatment program targeted to the positively identified patients. For HBV-HIV Coinfected patients, they will be monitored on their liver function test yearly for early detection of cirrhosis, end-stage liver disease, or hepatocellular carcinoma , and for HCV-HIV Coinfected patients, they will be treated with Hepatitis C antiretroviral treatment. [11, 20].

However, the incidence rate of Hepatitis B has increased from 2.26 per 100,000 in 2010 to 12.65 per 100,000 population in 2015 and majority are from IVDU [20] . Even with the introduction of Universal Hepatitis B Vaccination In Malaysia since 1989, the prevalence of HBV-HIV Co-Infection remains high among younger people less than 40 years old by 50.4% [20, 21].Internationally, there is also a suggestion on the administration of Hepatitis B revaccination to HIV-infected patients, by The German Standing Committee on Vaccination [22, 23]

As for HCV-HIV Coinfection, starting from 2019, the Ministry of Health has taken a step in making [illegible] in primary care centers. However, these prospects could be

counteracted by HCV reinfection due to on-going risk behaviours after successful treatment. Based on existing data from small and heterogeneous studies of interferon-based treatment, the incidence of reinfection after sustained virologic response range from 2–6/100 person-years among PWID to 10–15/100 person-years among Men Sex Men. [24]. Thus, by identifying the high-risk population for HCV-HIV Co-infection, a more frequent screening program need to be done later in HIV clinic instead of current yearly screening into six monthly screening and even post HCV treatment.[5]

In order to do a more targeted program, as suggested above, it is essential to update the information regarding the associated factor to this problem in the context of the local situation. There are few recent studies done nearby (Singapore) for Viral Hepatitis and HIV Co-infection, but not all the association studied in their research applicable to our situation since we have different sociodemographic background [25]. There is a lack of population-based study regarding HIV Co-infection in Malaysia, and the closest study was done using data from 2007-2012 at the tertiary care in Penang even though the decentralization of HIV treatment from the hospital started since 1997 [21]. Negeri Sembilan is chosen as site of study because it is the central region of Peninsular Malaysia with good coverage of Primary Care Clinics that offer HIV Clinics at all of it district. Thus this study aims to determine the prevalence and associated factors of Viral Hepatitis HIV Co-Infection (HBV and HCV) among newly registered HIV patient under government health facilities in Negeri Sembilan

Methods

A cross-sectional study from Negeri Sembilan HIV Case Registry (ARV line listing) contained the data regarding sociodemographic and clinical database of patients treated under government HIV clinics in Negeri Sembilan from January 2000 until March 2020 was done involving the 26 primary care (Klinik Kesihatan) and three tertiary care (hospital) in Negeri Sembilan. ARV linelisting is a surveillance data initiated and monitored by HIV Sector of Ministry of health regarding all HIV clinic services at state level starting from 2016.

Universal sampling was done involving all 1333 of HIV registered cases and sorted according to inclusion and exclusion criteria. The inclusion criteria of the study participant are patient aged 19 years old, newly registered patient under HIV Clinic of government healthcare facilities and the patient must be with a confirmed diagnosis of HBV and HCV with underlying HIV infection. The exclusion criteria were patient without an incomplete medical record. From this 1333 cases, we excluded 39 cases perinatal transmission, removed 14 duplicate cases and removed another 6 outlier cases with the remaining 1274 HIV patients left (Figure 1)

The sample size was calculated using a single population proportion formula using 4.1% for HBV-HIV prevalence [26] and 6.6% for HCV-HIV prevalence [25] . Using 95% confidence interval and 5% precision with attrition rate of 20%, a minimum of at least 70 participants with HBV-HIV Co-infection and 107 minimum participants for HCV-HIV Co-infection were required.

The data were entered and analysed using SPSS Version 25.0 statistical software. The primary outcome of the interest was either that HIV patients had HBV or HCV Co-infection or not. For univariable logistic regression analyses, crude odds ratio (OR) and 95% CI were calculated.

Multivariable logistic regression was used to determine independent risk factors associated with Co-infection, and the adjusted odds ratio (aOR) was calculated. All variables with $p < 0.05$ were retained in the final multivariable model. Subgroup interaction was done but not significant. Multicollinearity and model fits were also done to the model. Missing data of our two variables is less than 20% and treated using pairwise deletion.

No informed consent taken in this study as the data were only retrieved retrospectively from the database and no identifiers collected for this study.

Ethical approval for the use of the database (ARV line listing) was obtained from UiTM Ethical Board and Medical Research and Ethics Committee (MREC), Malaysia. NMRR No-19-3803-52335 (IIR).

Results

The prevalence of HBV co-infection among HIV-infected patients was 5.6% (71 cases), while the prevalence with HCV co-infection was 14.8% (189 cases). As for the frequency of multiple HIV-Coinfection, out of 238 HIV cases with Co-infection, majority, 70.17% were HCV-HIV Co-Infected followed by 20.5% were HBV-HIV Co-Infected while the rest of 9.24% were Co-Infected with HBV-HCV-HIV.

Epidemiological characteristics and clinical database of our study population were compared and described in four groups of HIV-infected patients: with mono-infection, co-infections with HBV only, co-infection with HCV only and HIV-HBV-HCV co-infections in Table 1. From our study population, the majority were infected by the HIV infection at the range of 30-39 years old (33.2%), single marital status (60.8%), and male in gender (80.4%).For Modes of Transmission, among homosexual,mostly have HIV monoinfection followed by HBV-HIV Co-Infection whereas among other modes of transmission,mostly have HIV monoinfection followed by HCV-HIV Co-infection. Among CD4 < 199 cell/mm3,mostly are HIV Monoinfection followed by HCV-HIV Coinfection followed by HBV-HIV Co-infection. Among Proffesional,mostly have HIV Monoinfection followed by HBV-HIV Co-Infection whereas among Non Professional,mostly have HIV Monoinfection followed by HCV-HIV Coinfection.

Table 1: Epidemiological characteristics of HIV-infected patients with mono-infection and HBV and HCV co-infections who attended the HIV clinic under government facilities from Jan 2000- March 2020 (N=1273)

Factors associated	HIV Mono-infected n(%)	Co-Infected with HBV Only n (%)	Co-Infected with HCV Only n (%)	Coinfected with both HBV and HCV n (%)	All n (%)
Age (years old)					
<29	331(86.4)	16(4.2)	33(8.6)	3(0.8)	383(100)
30 -39	335(79.2)	18(4.3)	61(14.4)	9(2.1)	423(100)
40-49	226(77.7)	11(3.8)	47(16.2)	7(2.4)	291(100)
>50	144(81.8)	3(1.7)	26(14.8)	3(1.7)	176(100)
Gender					
Female	239(96)	4(1.6)	6(2.4)	0(0.0)	249(100)
Male	797(77.9)	44(4.3)	161(15.7)	22(2.1)	1024(100)
Race					
Malay	650(76.5)	36(4.2)	144(16.9)	20(2.4)	850(100)
Chinese	192(92.8)	11(3.4)	6(2.9)	2(1)	207(100)
Others	194(89.8)	5(2.3)	17(.9)	0(0.0)	216(100)
Marital status					
Single	519(77.6)	36(5.4)	101(15.1)	13(1.9)	669(100)
Married	290(80.3)	11(3)	54(15)	6(1.7)	361(100)
Divorced	54(77.1)	1(1.4)	12(17.1)	3(4.3)	70(100)
Modes of Transmission					
Bisexual	54(96.4)	0(0)	2(3.6)	0(0.0)	56(100)
Heterosexual	577(91)	16(2.5)	35(5.5)	6(0.9)	634(100)
Homosexual	237(89.7)	20(7.5)	7(2.6)	2(0.8)	266(100)
IVDU	168(53)	12(3.8)	123(38.8)	14(4.4)	317(100)

CD4 Count					
<200 cells/mm3	295(73.9)	25(6.3)	71(17.8)	8(2.0)	399(100)
200-350 cells/mm3	241(82.5)	10(3.4)	35(12)	6(2.1)	292(100)
>350 cells/mm3	476(85.5)	13(2.3)	60(10.8)	8(1.4)	557(100)
Occupation					
Non-Professional	829(79.3)	41(3.9)	153(19.6)	22(2.1)	1045(100)
Professional	61(85.9)	7(9.9)	3(4.2)	0(0.0)	71(100)
Type of health facilities					
Hospital	594(85.5)	21(3.0)	72(10.4)	8(1.2)	695(100)
Primary care	442(76.5)	27(4.7)	75(16.4)	14(2.4)	578(100)
Source of cases					
Compulsory Screening	103(93.6)	2(1.8)	5(4.5)	0(0.0)	110(100)
Voluntary screening	177(83.5)	13(6.1)	19(9.0)	3(1.4)	212(100)
Diagnostic Screening	413(82.4)	27(2.4)	52(10.4)	9(1.8)	501(100)
High Risk Screening	220(68.1)	6(1.9)	87(26.9)	10(3.1)	323(100)

Simple logistic regression analyses indicated that among HIV infected patient, factors that significantly associated with the presence of HBV co-infection were: being male, Malay, acquired Co-Infection via IVDU transmission, patient with CD4 count less than 199 cells/mm3, seeking treatment at primary care and were diagnosed by diagnostic screening program via advice by the doctor .

In our multiple logistic regression analysis, it was found that being male (p = 0.014 : adjusted OR 3.629 (1.303,10.106), CD4 cells count less than 199 cells count (p = 0.016: adjusted OR 2.278 (1.288,4.028)and primary care (p=0.018 adjusted OR 1.825 (1.109,3.003) were significant (Table 2).

Table 2: Factors associated with Hepatitis B among newly HIV registered patient at Negeri Sembilan from Jan 2000- March 2020 (N=1273) (Multiple logistic regression)

Factors associated	Hepatitis B		Total frequency (N) %	p-value	Crude OR	95% CI	
	Yes	No				Lower	Upper
Age (years old)							
<29	20(5.2)	364(94.8)	384(100)				
30 -39	27(6.4)	396(93.6)	423(100)				
40-49	18(6.2)	273(93.8)	291(100)				
>50	6(3.4)	170(96.6)	176(100)				
Gender							
Female	4(1.6)	245(98.4)	249(100)	0.001	ref	ref	ref
Male	67(6.5)	958(93.5)	1025(100)	**0.014**	**3.629**	**1.303**	**10.106**
Race							
Malay	57(6.7)	794(93.3)	851(100)				
Chinese	9(4.3)	198(95.7)	207(100)				
Others	5(2.3)	211(97.7)	216(100)				
Marital status							
Single	50(7.5)	620(92.5)	670(100)				
Married	17(4.7)	344(95.3)	361(100)				
Divorced	4(5.7)	66(94.3)	70(100)				
Modes of Transmission							
Sexual	44(4.6)	912(95.4)	956(100)				
IVDU	26(8.2)	291(91.8)	317(100)				
CD4 Count							
Loading [MathJax]/jax/output/CommonHTML/jax.js		.5)	400(100)	**0.005**	**2.278**	**1.288**	**4.028**

200-350 cells/mm3	16(5.5)	276(94.5)	292(100)	0.347	1.38	0.706	2.697
>350 cells/mm3	21(3.8)	536(96.2)	557(100)	ref	ref	ref	ref
Occupation							
Non-Professional	64(66.5)	982(93.9)	1046(100)				
Professional	7(9.9)	64(90.1)	71(100)				
Type of health facilities							
Hospital	29(4.2)	666(95.8)	695(100)	ref	ref	ref	ref
Primary care	42(7.3)	537(92.7)	579(100)	**0.018**	**1.825**	**1.109**	**3.003**
Source of cases							
General Population	2(1.8)	108(98.2)	110(100)				
Screening							
Voluntary Screening	16(7.5)	196(92.5)	212(100)				
Diagnostic Screening	37(7.4)	465(92.6)	502(100)				
High-Risk Screening	16(5)	307(95)	323(100)				

*Test used: Multiple Logistic Regression Analysis (Method Backward LR: B constant = 4.467,Model assumption are met: Interaction not significant in model, No Multicollinearity)

Note: AOR=Adjusted Odd Ratio, CI: Confident Interval, Nagalkerke R2=0.055,Hosmer and Lemeshow test= 0.87 Classification = 94.4 % correct, Area under ROC= 66.6.

Factors that significantly associated with the presence of HCV-Coinfection in univariable logistic regression were being male in gender, age of 30-39 or age 40-49, Malay, IVDU modes of transmission, CD4 count less than 199 cells/mm3, non-professional type of occupation, seeking treatment at primary care and were diagnosed by high-risk screening at methadone or prison screening.

In multivariable logistic regression, only Gender (p<0.001;adjusted OR 6.860(2.657,17.711),Malay Race

), IVDU risk factor (p<0.001; adjusted OR 6.802

(4.458,10.379)), high-risk screening source of case (p <0.001; adjusted OR 4.199 odds (95%CI:1.536,11.476) are significantly associated with the HCV-HIV Co-Infection outcomes of the study population. (Table 3)

Table 3: Factors associated with Hepatitis C among newly HIV registered patient at Negeri Sembilan from Jan 2000- March 2020 (N=1273) (Multiple logistic regression)

Factors Associated	Hepatitis C		Total frequency (N) %	p-value	Adjusted OR	95% CI	
	Yes	No				Lower	Upper
Age (years old)							
<29	36(9.4)	348(90.6)	384(100)	0.004			
30 -39	70(16.5)	353(83.5)	423(100)	0.003			
40-49	54(18.6)	237(81.4)	291(100)	0.001			
>50	29(16.5)	147(83.5)	176(100)	0.016			
Gender							
Female	6(2.4)	243(97.6)	249(100)	ref	ref	ref	ref
Male	183(17.9)	842(82.1)	1025(100)	<0.001	6.860	2.657	17.711
Race							
Malay	164(19.3)	687(80.7)	851(100)	<0.001	**4.098**	**1.893**	**8.871**
Chinese	8(3.9)	149(96.1)	267(100)	ref	ref	ref	ref
Others	17(7.9)	199(92.1)	216(100)	0.077	2.443	0.909	6.568
Marital status							
Single	114(17)	556(83)	670(100)				
Married	60(16.6)	301(83.4)	361(100)				
Divorced	15(21.4)	55(78.6)	70(100)	0.614			
Modes of Transmission							
Sexual	52(5.4)	905(94.5)	957(100)				
IVDU	157(49.5)	180(57.4)	317(100)				
CD4 Count							
<199	79(19.8)	321(80.3)	400(100)				

200-349 cells/mm3	41(14)	251(86)	292(100)				
>350 cells/mm3	68(12.2)	489(87.8)	557(100)				
Occupation							
Non-Professional	175(16.7)	871(83.3)	1046(100)				
Professional	3(4.2)	68(95.8)	71(100)				
Type of health facilities							
Hospital	80(11.5)	615(88.5)	695(100)				
Primary Care	109(18.8)	470(81.2)	597(100)				
Source of cases							
General Population	5(4.5)	105(95.5)	110(100)	ref	ref	ref	ref
Screening							
Voluntary Screening	22(10.4)	190(89.6)	212(100)	0.231	1.908	4.458	10.379
Diagnostic Screening	61(12.2)	441(87.8)	502(100)	0.433	1.490	0.550	4.033
High-Risk Screening	97(30.0)	226(70)	323(100)	**0.005**	**4.199**	**1.536**	**11.476**

*Test used: Multiple Logistic Regression Analysis (Method Backward LR: B constant 6.241 ,Model assumption are met: Interaction not significant in model, No Multicollinearity) Note: AOR=Adjusted Odd Ratio, CI: Confident Interval, Nagalkerke R2= 0.372,Hosmer and Lemeshow test= 0.229 Classification = 85.2 correct, Area under ROC = 84.9%

Discussion

The prevalence

The prevalence of HBV-HIV Co-infection among HIV-infected patients was 71 cases (5.6%). This prevalence is similar to countries of low endemicity, such as Ethiopia (5.6%) [27]. In Southeast Asia, the

mated to be 10.4%, and our prevalence is lower when to

compare to the specific neighboring country of such as Singapore with their prevalence is (7.7), Thailand (3.3 to 13%) and Indonesia (3.2-15.3%) [25, 28, 29]

The prevalence of HCV-HIV Coinfection in our study was 14.8, which quite similar to the prevalence in Southeast Asia at 15.2% [6]. Comparing to other nearby countries, we were higher than Cambodia (5.5%) Myanmar (5.3%), Thailand (5.1%), Singapore (7.7%), but lower compared to countries such as Vietnam (42.5%) and Indonesia (17.9%) [30]. Globally in the US, the prevalence rates of HCV-HIV Co-Infection were higher at 25-50% [31].

In comparing our study finding for both HBV-HIV and HCV-HIV Coinfection to the latest and nearest study at a tertiary hospital in Malaysia by (Akhtar, Khan, et al. 2016), their HBV-HIV Co-infection prevalence was 13%, and HCV-HIV Co-infection was at 18.4 % respectively which was higher than in our study. [21] This might be due to few reasons such for instance, our study was more population-based, which covers both primary care and tertiary care; thus, the burden of HIV Co-Infection was lesser compared to studying in tertiary care only. Comparing to Penang, their documented numbers of AIDS cases itself from 1986-2015 were higher at 1155 numbers of cases compared to Negeri Sembilan, which only has 1003 numbers of cases [32]. Generally, such HIV Co-Infection prevalence differences could be due to differences in geographic regions, HBV vaccination rates, predominant modes of transmission, and prevalence of HBV and HCV in the general population as what several studies reported in different parts of the world, [28, 33]

As for the frequency of multiple HIV-Coinfection, out of 238 HIV cases with Viral Hepatitis Co-Infection, the majority were HCV –HIV Co-Infected cases followed HBV-HIV Co-Infected cases while the least were Co-infected with HBV-HCV-HIV cases. This majority is similar when compared to a study in Vietnam by (Huy, Vernavong, et al. 2014) [34].This similar prevalence result was due to both Malaysia and Vietnam has high proportion of HCV cases from IVDU s by 59% and 89.5-98.5% respectively [20, 28]. Malaysia was also ranked as the third country with the highest HIV prevalence after Vietnam among the Western Pacific Region in 2017 [35].

Our finding was, in contrast, to study by Singapore and Gondar, where the majority were coinfected with HBV-HIV, followed by HCV-HIV, and the least were coinfected with all HBV-HCV-HIV Co-infection [25, 27]. In Singapore, the reduction in numbers of IVDUs was due to the government's aggressive campaign and strict penalty, which leads to a lack of drug supply. Subsequently, this reduces the prevalence of HCV-HIV Co-Infection in that country[36].

HBV-HIV Co-Infection

Gender is a significant factor associated with both HIV-Coinfection and contributor to both predictive modelling. Males' gender has 3.629 odds (95% CI: 1.303,10.106) getting HBV-HIV than female, and this is consistent with studies done at Southeast Asia, Singapore and Tertiary Hospital in Penang [6, 21, 25]. Female HBV carriers have lower viral loads than male carriers, and the prevalence of serum HBV surface antigen (HBsAg) has been reported higher in men than in women [37, 38]. Moreover, majority of those that homosexual (42%), and some studies claimed that multiple

partners were more common among homosexual men and anal sex is usually more traumatic than vaginal intercourse, resulting in an increased risk of exposure to blood transmission of HBV disease [4, 39]

HBV-HIV Co-Infection patients that have CD4 <199 cells/mm3 prone by 2.278 odd to get HBV-HIV (95% CI: 1.288,4.028) compared to those with CD4 >350 cells/mm3 in which is consistent with the study finding by Chen et al. 2016 [29]. Co-infection of HIV and HBV can cause complex interactions because HIV impairs the cellular immunity, leading to increased replication of HBV, this increase in viral replication of HIV and HBV can further contribute to the impairment of the immune system [40]. In general, studies showed an association between lower baseline CD4 cell count and HBV co-infection [12, 27, 41, 42]. Most of our viral hepatitis-HIV Co-infection patient are males and generally, the CD4 level among male is lower than female due to the daily activities of men who spend more time to do hard work for an extended period as well as men also more prone to stress, and these may contribute for lower CD4 count. [27]

Our study showed that HIV patients have 1.825 times odds (95% CI: 1.109,3.003) to be diagnosed as having the HBV-HIV co-infection at primary care rather than in the hospital. This determinant is a good reflection of how our adequate primary care provides good accessible services for HIV patients to do screening for Viral Hepatitis disease. Most of our HBV-HIV infected patients were infected via sexual transmission, where 60% of the cases were diagnosed at Primary Care. Out of this, 48% of the cases were diagnosed at Klinik Kesihatan Seremban under the special program as Sexual Transmitted Infection (STI) friendly clinic. The formation of STI friendly clinic was an initiative started since January 2016 did help much in capturing the HBV-HIV co-infection cases, which mainly contributed by sexual transmission [43]. Few studies showed that screening activities at the STI clinic detected many HBV, HCV, and HIV cases, which warrants specific preventive action to be done there. [44]

More cases of HBV-HIV infection were detected in primary care also due to the availability and accessibility to the service subsequently after the initiative done by the Ministry of Health to decentralized HIV treatment to primary care since 23 years ago. Successively, more medical doctors and family health medicine specialists are more competent in handling HIV cases well even provides more personalized care at primary care level, and this attracted many vulnerable groups for HIV to come out for the screening test and treatment. Furthermore, a systematic study found that the aspect of health care most valued by HIV patients was healthcare, which provides easy access for appointments and experienced and interactive doctors. Thus, our decentralization of services to primary care is a good initiative. [45].

In contrast, in some studies, hepatitis co-infection was not associated with increased primary HIV care utilization. It was because they utilize other subspecialty services, such as gastroenterology or hepatology, and due to evolving guideline recommendations for less frequent monitoring for patients with well-controlled HIV disease.[46] The difference between their findings and our study is that Malaysia has a different and good primary care system with less referral to the specialty in the hospital due to the training that we have to our specialist in primary care [47]. In the future, we hope that with the availability

of excellent services in our primary care, more primary prevention can be done, which subsequently reduces the burden of Viral Hepatitis-HIV Co-infection diseases as what it supposed to be.

Male gender, CD4 level less than 199 cells/mm3 and primary care type of facilities was the significant factor in the modeling to predict the outcome of HBV-HIV Co-Infection, and a focused targeted intervention strategy should be based on this. Thus, our recommendation of HBV revaccination should be made at primary care facilities to a mainly male patient with a low CD4 level than <199 as they are more prone to HBV-HIV. However, the patient's CD4 must be lifted to more than 350 cell/mm3 before the revaccination of Hepatitis B [22, 23, 48].

Hepatitis B revaccination has been recommended for MSM, IVDU, and heterosexuals with a recent history of a sexually transmitted disease or multiple sex partners by Europe Communicable Centre and many other countries [5, 49]. The recommendation for Hepatitis B revaccination for IVDU in the large scale HIV prevention program was also suggested to the countries that have a high HIV burden coming from IVDU key population. [34].

Since the type of facilities at primary care as one of the significantly associated determinants with HBV-HIV Co-infection, these facilities serve as a good avenue for the revaccination program and should be done for the targeted group mentioned above. The successful outcome of HIV infected patients will require not only appropriate antiretroviral and antiviral therapy, but also sustained attention to long-term treatment toxicities, non-HIV-specific comorbid conditions (e.g., substance abuse, psychiatric illness), and comorbid behaviors (e.g., adherence, diet, and exercise) [50]. Thus, a more holistic approach should be given to the high-risk group to prevent them from getting HBV-HIV Co-Infection at the primary care setting.

HCV-HIV Co-infection

As for HCV-HIV Co-Infection patients, males have 7.725 odds (95%CI: 2.982, 20.013) of getting the co-infection than females, which is consistent with the finding by study at Southeast Asian and study at a tertiary hospital in Penang [21, 29]. In HCV-HIV Co-Infection, the female genetics made them have a spontaneous clearance of the infection of HCV, and the female hormone of estrogen is protective for the liver from progress to chronic HIV [51, 52]. Besides, the majority of modes of transmission for HCV-HIV Co-Infection were IVDU (74%), and it was proven that most of the IVDU were men [30]. Even though only a small percentage of the cases in HCV-HIV is due to the homosexual transmission in our study (6%), they were still at a higher risk of contracting HCV-HIV Co-Infection due to the practice associated with mucosal trauma and recreational drug use [53]. Furthermore, one study also found that HCV-HIV coinfected men were more likely than HIV-uninfected men to shed HCV RNA in semen[54]

Malay has 4.098 times odd to get HCV-HIV (95%CI: 1.893,8.871) compared to Chinese, and this was consistent with the study finding at Singapore and Penang even though both studies have Chinese as most of their study population races. Generally in Malaysia, Malay constitute the majority of the sociodemographic by 61.7% followed by Chinese 20.8% and the majority of Malaysian IVDU by 2018

were Malay by 20,671 (80%) numbers followed by Chinese at 1480 (6%) in numbers [55], and this explained why in our population-based study, Malays were more prone for HCV-HIV Co-Infection.

IVDU has a higher odd of 5.916 to get HCV-HIV (95% CI 3.875,9.034) compared by sexual modes of transmission. These odds were higher when comparing to the nearest local study by Akhtar, Khan, et al. 2016, which found that IVDUs have 2.376 odds (95%CI: 1.541,3.664) to get the HCV-HIV Co-Infection. Globally, our finding is consistent with the finding by Choy, Ang et al. 2019 and Chen et al. 2016 and, where IVDUs have 10.15 to 34 times odds for HCV-HIV Co-Infection [6, 21, 25]. Sharing needle is acknowledged as the main route of HCV acquisition among IVDU from the direct percutaneous exposure to contaminated blood from a needle, and this risk also depends on the quantity of blood inoculated and the viral load of that person has.[24] The risk is higher in people with HIV infection, thus made them highly infectious. [56]

High-risk screening programs in prison and methadone have 4.312 odds (95%CI: 1.571,11.838) in detecting the HCV-HIV Co-Infection than usual population screening. Among the HCV-HIV positive patient from the high-risk screening program,79% were from the prison screening program, whereas another 21% were from the methadone screening program. Screening of HIV program in Malaysian prison was started since 1990, with the latest guideline in 2002 which suggest screening of HIV on entrance into the prison, followed by 3 or 6 months before discharged without no screening in during the imprisonment. Once the patient detected HIV positive, they will be referred to the nearest hospital were at the same time will be screened for HCV and HBV, followed by treatment if indicated.[57]

High-case detection in prison was that prisoners often come from vulnerable strata of society suffering from poor health with few health opportunities. Besides, they also have a high probability of engaging in injecting drug practice and sexual risk behaviors even before the incarceration [58]. When in imprisonment, these concentrations of individuals coming from high-risk environments may remain their high-risk behaviors even in the correctional institute, making it a critical setting for transmission of HCV infection [59].A study by (Treloar, McCredie, et al. 2015) suggested that the potential for transmission of hepatitis C virus (HCV) in prison settings was well established and directly associated with the sharing of injecting and tattooing equipment, as well as physical violence.[60]

Even though in our study we cannot determine the exact onset of the HCV-HIV infection occurred either before imprisonment or during the imprisonment, the above evidence showed that HCV-HIV infection could occur at both stages along with the evidence that the Malaysian recidivism rate is 16.7% from all the prisoners.[61]

Male, Malay, IVDU risk factor, and high screening source of cases are significant factor in the modeling to predict the outcome of HCV-HIV infection. Since the Hepatitis C treatment has been decentralized to primary care, we expect the reinfection can occur if this high-risk behavior continues. Evidence suggested that high rates of HCV reinfection after spontaneous clearance or treatment in HIV positive MSM even more higher than IVDU thus targeted intervention in both group should be emphasized [24, 62]

A more targeted and outreach approaches are also needed for IVDU and MSM because stigmatization limits their access to testing and treatment [30]. Studies suggested that guideline of screening and access to testing and treatment was challenging and poorly implemented primarily in a low-income country and middle-income setting as well in the population such IVDU, prisoners, site worker and MSM [63, 64]. Thus, a proper counseling and strategies should be given along with a more frequent screening of HCV during pre and post HCV treatment for them especially IVDU from the prison. The prevention of the Hepatitis C program at prison should be done , including yearly voluntary and compulsory testing instead of testing during the enrollment and before release from prison only [5, 65]. The positive HCV-HIV patients are encouraged to be treated while in the prison program, as it was suggested to be more efficient [66].

Limitation And Recommendation

Our study was a cross-sectional study design; thus, it was unable to supplement the information with prospectively collected data and only determine the association but not the causation. Variables such as educational level, monthly income, alcoholic status, immunization status (previous immune status to Hepatitis B), and time first tested positive for HBV/HCV before HIV diagnosis cannot be gained as it would be a valuable variable to be added in this study.[21, 25, 67].Lack of this important variable leads to patients who had been tested positive with HBV and HCV co-infection more than one year before their HIV diagnosis could have been misclassified as having acute infection. The introduction of new variables in our study also might result in misclassification of data to happen as we have fewer references as a guideline. Our study data also only involved HIV population under government healthcare facilities care in Negeri Sembilan state only, therefore it will not represent the whole Malaysian country population and the low proportion of patient with HBV-HIV infection in Negeri Sembilan might affect the true estimation of the disease burden

A proper cross sectional study with good generalizability should be conducted since the finding in our study population-based in Negeri Sembilan was found to be different from the closest study in Penang tertiary hospital study only. This improved country-level data, particularly in countries where the growing population of People Who Inject Drugs (PWID) and a concentrated epidemic of PWID and MSM large owning to HIV infection are needed to help define their epidemiology and inform Policies of Hep C testing. A more depth study regarding HIV-Coinfection and their accessibility to treatment should be done at the prison to see the real situation and the applicability of doing prevention programs there.

Conclusions

Since the past ten years, the HIV modes of transmission has been changed from IVDU into the sexual transmission, but the prevalence of HCV-HIV in our study which mostly coming from IVDU is still higher compared to HBV-HIV Co-infection, and the majority of the cases were IVDU from high screening program. Thus a targeted program still should be aimed at these determinants. The availability of HCV [illegible] to reduce the burden of this disease; however, a more

effective primary prevention program should be given, especially among the vulnerable HIV population at the prison who have a higher risk of detected with the HCV-Co-infection. In the absence of the HCV vaccine, a more focused intervention on behavioural intervention and linking of testing to treatment should be done as apart of HCV control efforts in Malaysia. As for the HBV-HIV Co-infection, our population prevalence was lowered compared to other countries' prevalence but more concentrated from those with sexual transmission modes of transmission. Thus, we would suggest revaccination of Hepatitis B to be done to those prone to get this HBV-HIV Co-infection as what other developed countries have been doing. We also need to enhance our primary prevention activities at primary care as this are the significant accessible healthcare centre to these populations.

Abbreviations

ARV -Antiretroviral

HIV- Human Immunodeficiency Virus

HBV - Hepatitis B Virus

HCV- Hepatitis C Virus

IVDU- Intravenous Drug User

KK-Klinik Kesihatan (Community Clinic)

MSM- Men Sex Men

PWID-People Who Inject Drug

PLHIV-People Living with HIV

RDT-Rapid Diagnostic Test

STI-Sexual Transmitted Disease

Declarations

Ethics approval and consent to participate

Ethical approval for the use of the database (ARV line listing) was obtained from UiTM Ethical Board and Medical Research and Ethics Committee (MREC), Malaysia. NMRR No-19-3803-52335 (IIR).

No informed consent taken in this study as the data were only retrieved retrospectively from the database and no identifiers collected for this study

Not applicable

Availability of data and materials

All data supporting the study findings are within the manuscript. Additional details information and raw data are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no competing of interest regarding this study.

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Authors' contributions

Siti Aishah Abas and Ahmad Taufik Jamil conceived the project. Siti Aishah Abas and Sharifah Nor Ahmad contributed in the data collection.Siti Aishah Abas,Ahmad Taufik Jamil,Mohd Shahril Ahmad Saman and Mariam Mohammad contributed in data analysis. The manuscript was written mainly by Siti Aishah Abas with approval of all authors. All authors read and approved the final version of manuscript for publication.

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Figures

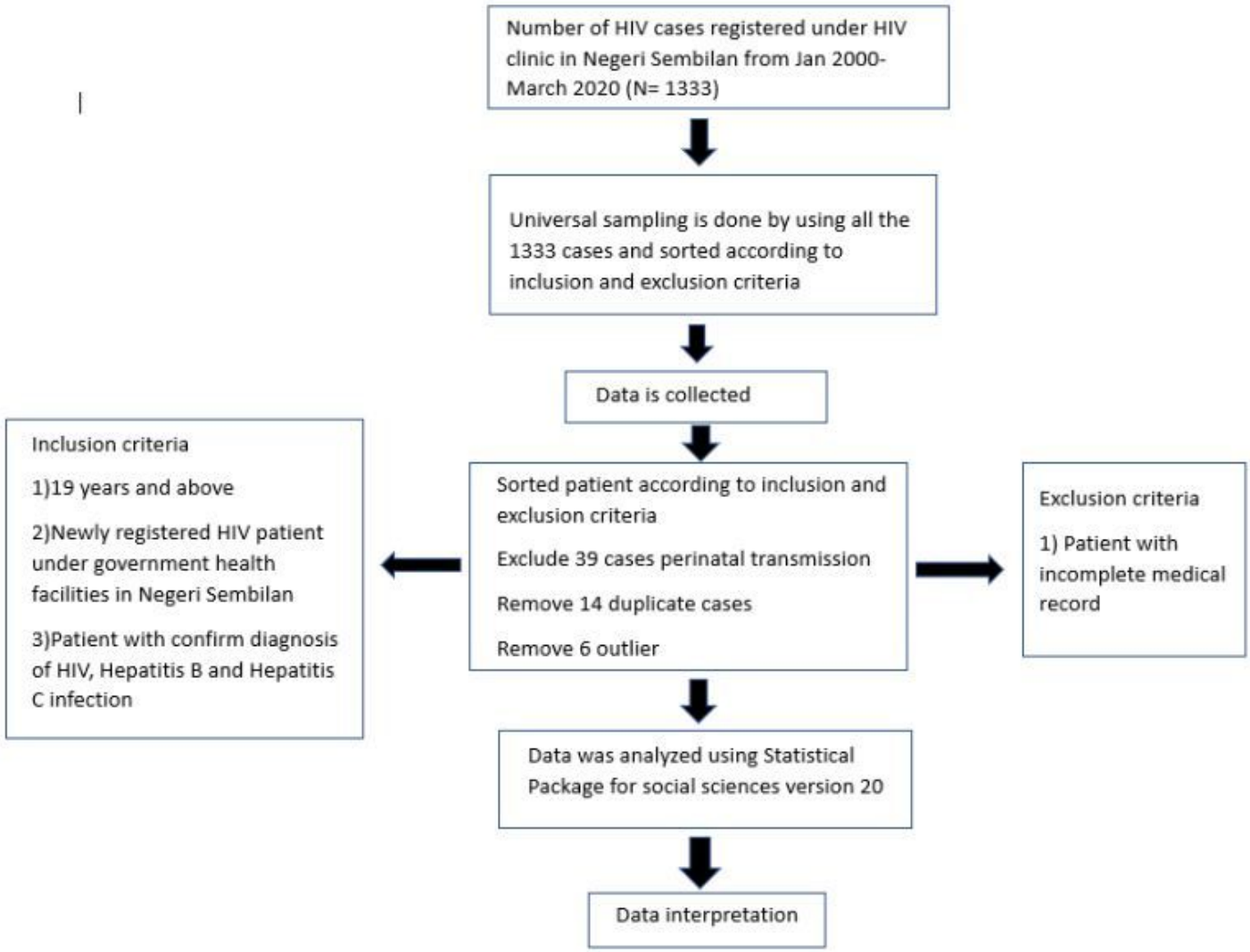

Figure 1

Flow of the study

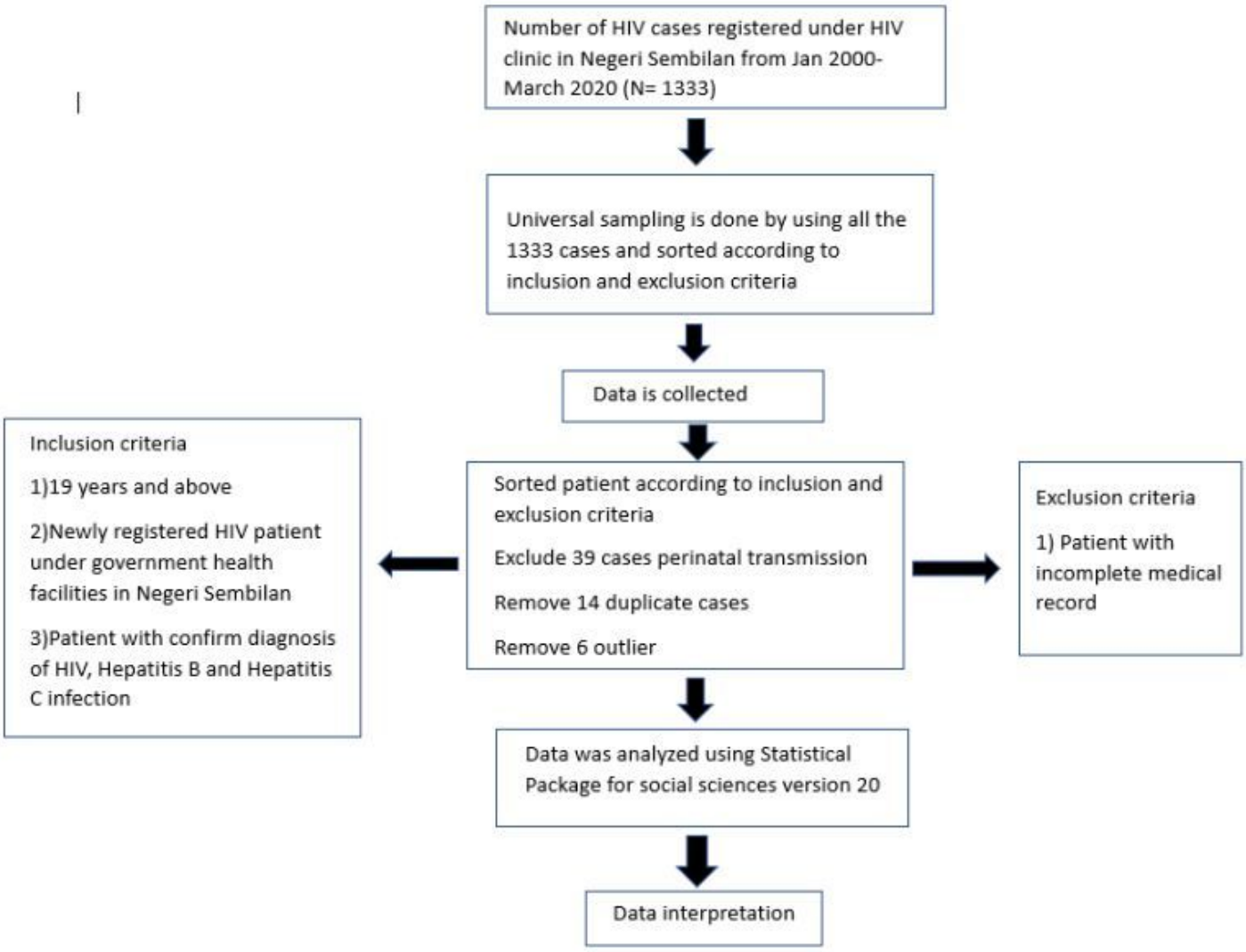

Figure 1

Flow of the study

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