Epidemiological features and risk factors for acquiring Hepatitis B, Hepatitis C and syphilis in HIV-infected patients in Shaanxi Province, northwest China

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Research article

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Abstract

Background HIV-infected patients are at higher risk for co-infection with Hepatitis B virus (HBV), Hepatitis C virus (HCV), and Treponema pallidum (TP), the agent causing syphilis, than the general population. The prevalence of HBV, HCV, and syphilis had geographic differences and varied from region to region among HIV-infected patients. The aim of this study was to investigate the epidemiological features and risk factors of HBV, HCV, and syphilis infection in HIV-infected individuals in Shaanxi Province, northwest China. Methods A retrospective study was conducted with HIV-infected patients from June 2011 to June 2016 in Shaanxi Province. Sociodemographic data was captured from the national HIV/AIDS information system in China. Serological tests and analysis of CD4+ T-cell count levels were performed using standard procedures. Besides, the HIV infection time and age were presumed by CD4+ T-cell count levels. Results The average time from HIV infection to diagnosis was (4.7±2.4) years, and the HIV infection time ≥3 years accounted for 66.8%. Of the discovery routes, voluntary counseling & testing (VCT) only accounted for 20.7%. Among 1018 HIV-infected patients, the prevalence of HBV, HCV, and syphilis was 11.0%, 11.1%, and 26.0%, respectively. HBV-HCV, HCV-syphilis, HBV-syphilis, and HBV-HCV-syphilis co-infection was 1.7%, 2.2%, 2.6%, and 0.1%, respectively. The rate of ineffective vaccination against HBV was as high as 30.2% in HIV-infected patients. Ethnicity (OR=29.257, 95%CI: 11.243-76.133) and HIV transmission routes (OR=149.368, 95%CI: 16.590-1 344.861) were the risk factors of HCV infection in HIV-infected patients. In the HIV-infected patients with the antibody of Treponema pallidum, the rate of homosexual transmission was so higher but heterosexual transmission is lower (OR=0.548 95% CI: 0.382-0.786), suggesting that homosexual transmission might be a risk factor for HIV-syphilis co-infection. Conclusion The HIV-infected patients in Shaanxi Province had the characteristics of low active detection rate and late diagnosis. In addition, a high prevalence of HBV, HCV, and syphilis co-infection could be observed, and like HIV infection, they might not understand their HBV, HCV and syphilis infection status. At last, the high rate of ineffective vaccination against HBV suggests a need for improved vaccination services.

Background

Retinal vein occlusion (RVO) is a retinal vascular disorder characterized by obstruction of the retinal venous system, often associated with hypertension and coagulation abnormalities [1, 2]. It is a common cause of visual handicap in the elderly throughout the world[3], and could be subdivided into central RVO (CRVO),branch RVO (BRVO) and hemi RVO (HRVO) according to the location of blockage[4]. Moreover, both CRVO and BRVO can be further classified into non-ischemic subtype and ischemic subtype based on the amount of retinal capillary perfusion [5]. Macular edema (ME) is one of the prominent complication in patients with ischemic RVO and can cause severe impairment of central vision [6]. Various treatment modalities had been used to treat ME, anti-vascular endothelial growth factor (VEGF) therapy had been demonstrated to be safe and effective among these available therapies [7-10].

The eyes with RVO may have abnormal choroidal vasculature, due to hydrostatic pressure and VEGF level [11]. Several studies had investigated subfoveal choroidal thickness (SFCT) in CRVO eyes and BRVO eyes, however, the results were contradictory. Some studies found that SFCT of affected RVO eyes had no significant difference compared with that of unaffected fellow eyes [11]. However, other studies showed that SFCT of RVO eyes was significantly thicker than that of unaffected fellow eyes [12] [13]. Besides, SFCT change after anti-VEGF therapy was also contradictory [14, 15]. Most of the studies reported that the SFCT was decreased significantly after anti-VEGF treatment[12, 16], while a few studies reported that SFCT didn't decrease after anti-VEGF treatment [9]. Thus, these contradictory results warrant further investigation.

VEGF level was demonstrated as the principal factor which contribute to SFCT change.[11] Elevated VEGF expression could lead to increased capillary permeability and leakage in retina and choroid [2, 17], is critically involved in the pathogenesis of ME secondary to RVO [18, 19]. Franco-Cardenas and colleagues found that ischemic index in CRVO was much higher than that in BRVO [20], what is more, Yasuda and colleagues found that aqueous VEGF concentration in CRVO eye was significantly higher than that in BRVO eye [21], these studies suggested that retinal ischemia in CRVO was more severe than that in BRVO. Therefore, we assume that SFCT of CRVO eye may be thicker than that of BRVO eye, however, it is uncertain and need to be demonstrated.

The present study was aimed to further investigate the SFCT in CRVO and BRVO eyes respectively, and to evaluate its short term response after a single IVR injection. More importantly, to compare SFCT and SFCT change after IVR injection between CRVO eye and BRVO eye.

Methods

In the retrospective case series, we collected and evaluated the data of thirty-six patients with unilateral ME secondary to RVO. Nineteen patients had CRVO, and seventeen patients had BRVO. The diagnosis was determined according to the fundus examination and fluorescein angiography. Inclusion criteria were as the follows: (1) the age ranged from 50 to 70 years; (2) recent-onset (less than 1.5 months) and treatment-naïve when presented to the hospital; (3) was ischemic subtype and had received at least one intravitreal ranibizumab injection after newly diagnosed; (4) had follow-up of at least 2 weeks; (5) had comprehensive ophthalmic examinations before and after treatment. Patients were excluded if their fellow eyes had any macular disorder such as age-related degeneration (AMD), polypoidal choroidal vasculopathy (PCV) or central serous chorioretinopathy (CSC). Patients were also excluded if the affected eyes or fellow eyes had any of the following criteria: (1) axial length > 26.00 mm or < 22.00 mm; (2) a history of pars plana vitrectomy or other intraocular surgeries within half year. The present study followed the tenets of the declaration of Helsinki and was approved by the ethics committee in hospital. The subjects had been informed written consent on the study.

Data collected from patients' medical records included age, axial length, gender, systemic diseases, and SFCT value at baseline and after two weeks of IVR injection. All patients had undergone standardized ophthalmic examinations, including best-corrected visual acuity (BCVA), intraocular pressure (IOP), slit-lamp biomicroscopy, funduscopic, fluorescein angiography (Heidelberg retina angiograph; Heidelberg Engineering Inc., Dossenheim, Germany), and enhanced depth imaging optical coherence tomography (EDI-OCT) (Heidelberg Engineering Inc,Dossenheim, Germany). BCVA was measured by the Early Treatment Diabetic Retinopathy Study (EDTRS). They had received intravitreal ranibizumab injection (Lucentis, 0.05ml, 0.5 mg) after newly diagnosed. After that, the following treatment strategies were varied based on clinically relevant benefits and risks, patients' anticipated visiting compliance, and the factor that whether the patients could afford the cost of ranibizumab. During the follow -up period, some of the patients were administered IVR injection monthly for three times, others received corticosteroids injection or laser photocoagulation. nine patients with CRVO had received continuous IVR injection monthly for three times, whereas six patients with BRVO had received this treatment regimen. There were eight patients in both CRVO and BRVO groups who were administered corticosteroids injection or laser photocoagulation due to cost issue. Besides, five patients (including two CRVO and three BRVO) had lost to follow-up.

The demographic characteristics and SFCT value were collected. SFCT was measured from the outer border of the pigment epithelium to the choroidal scleral boundary, it was measured by 2 observers independently, and was recorded with the mean value. Statistical analysis was performed using Statistical Package for Social Science (SPSS) software (version 20.0, SPSS, Inc, Chicago, IL, USA). Continuous variables of the demographic characteristics were displayed as mean± standard deviation (SD), categorical variables were displayed as the number of subjects and its percentage. Difference between continuous variables was analyzed by independent *t* test, and Chi-square test was used for categorical variables. The SFCT values were displayed as mean± standard deviation (SD). The paired *t*-test was used to determine the difference in SFCT between RVO eye and its fellow eye. The SFCT between pre-injection and post-injection was also compared by paired *t*-test. The SFCT and SFCT change were compared between CRVO eye and BRVO eye by independent *t*-test. P value <0.05 was considered statistically significant.

Results

Choroidal thickness was associated with the demographic characteristics of subjects. Axial length is an important predictor factor for the macular choroidal thickness, previous studies had demonstrated that the eyes with longer axial length would have thinner choroidal thickness [22, 23]. Age is another important factor, previous studies reported that choroidal thickness would decrease 10-15μm [24] or 20- 26μm [25, 26] with age getting each 10 years older. As is summarized in table 1, no statistically difference was founded in axial length and age between CRVO group and BRVO group ($p<0.05$, independent *t* test), suggesting that the two groups were well balanced on axial length and age. Besides, there were no difference in gender distribution and smoking percentage between the two groups ($p<0.05$, Chi-square test). The

percentage of systemic diseases (such as hypertension, diabetes, and abnormal coagulation) had no statistically difference between the two groups. Additionally, the BCVA and IOP at baseline were shown in table 1, no significant difference was found between CRVO and BRVO group.

The retrospective analysis of laboratory records identified 1018 individuals with HIV infection from June 2011 to June 2016 at Shaanxi Provincial Center for Disease Control and Prevention, whose average age was 36.0±13.2 years old, ranging from 2 to 83 years old. And their median age was 34.0 years old. The age distribution was mainly concentrated in 20-50 years old, accounting for 80.6%. And ethnicity groups of the 1018 HIV-infected patients included Han Nationality (91.5%), Yi Nationality (7.0%), and others (1.6%). The most patients (46.8%) in this study had married with spouse. More than 64.1% of patients had low literacy (Junior high school level and below). And HIV infection was mainly transmitted through sexual contact (90.7%), including heterosexual transmission (65.5%) and homosexually transmission (25.1%) (Table 2).

CD4+ T-cell count and estimation of HIV infection time and age

Of 1018 HIV-infected patients, 714 were tested for CD4+ T-cells within one year of diagnosis, accounting for 70.1%. According to the rule that the CD4+ T-cell count was reduced by an average of 50/μL per year, the infection time ≥ 8 years accounted for 25.2% (180/714), in 5-8 years accounted for 23.2% (166/714), in 3-5 years accounted for 18.3%(131/714), and <3 years accounted for 33.2% (237/714).

The average age of infection in the 714 patients was 31.0±13.1 years old. The average time from HIV infection to diagnosis was 4.7±2.4 years. The average infection time of ≥50 years old group was 5.7 ± 2.4 years, which was significantly higher than that of <50 years old group (4.6 ± 2.4 years) (t=4.500, p<0.01).

Source of blood samples in 714 HIV-infected patients who completed CD4+ T cell test within one year of diagnosis

The sample source of 714 HIV-infected patients completed CD4+ T cell test within one year of diagnosis were shown in Table 3.

The recent HIV infection rate in HIV-infected patients ≥ 50 years old

A total of 154 HIV-infected individuals ≥ 50 years old underwent recent infection test, of which, 13.6% (21/154) were diagnosed with recent HIV infection (Infection time is less than 130 days.).

The prevalence of HIV-infected patients co-infected with HBV, HCV, and syphilis

Of 1018 HIV-infected patients enrolled in this study, the prevalence of HBV, HCV, and syphilis was 11.0%, 11.1%, and 26.0%, respectively. And the prevalence of HBV-HCV, HCV-syphilis, HBV-syphilis, and HBV-HCV-syphilis was 1.7%, 2.2%, 2.6% and 0.1%, respectively (Fig.1).

Prevalence of HBV serum markers

19 kinds of HBV marker's phenotype distribution were found. Of which, 43.8% were isolated HBsAb positive, and 30.2% were negative for HBV markers. 1.6% were positive for HBsAg, HBeAg and HBcAb, while 2.9% were positive for HBsAg, HBeAb and HBcAb.

The positive rate of HBsAg in Yi Nationality (18.3%) was higher than that of Han Nationality (10.5%), and the rate of active acute HBV infection in Yi Nationality (5.6%) was significantly higher than that in Han Nationality (1.3%) (p<0.05),

Risk factors of HIV-HCV and HIV-syphilis co-infection

Risk factors observed by the chi-square analysis such as ethnicity, marital status, education level, and HIV transmission routes were used as factors that might affect HCV infection (p<0.05) (Table 2). Multivariate logistic regression analysis was conducted using stepwise regression analysis. The results showed that ethnicity, education level, and HIV transmission route were the risk factors of HCV infection in HIV-infected patients (Table 4). Factors such as age, gender, education level, and HIV transmission routes were considered factors that may affect syphilis infection (Table 2). Multivariate logistic regression analysis was performed. The age and transmission routes were the risk factors for syphilis infection in HIV-infected individuals (Table 5).

Representative EDI-OCT images of CRVO are shown in Fig 1A, B and C. Compared with unaffected fellow eyes, the SFCT of CRVO eyes was significantly thicker than that of fellow eyes, the mean SFCT of CRVO and fellow eyes were 326.03±30.86μm and 249.29±31.55μm, respectively (p<0.001,paired *t* test). However, after 2 weeks of IVR injection, the mean SFCT of CRVO eyes reduced to 294.15±30.83μm, which was significantly thinner than that before treatment (Fig 1D, p<0.001, paired *t* test).

Similarly the SFCT of BRVO eyes was significantly thicker than that of fellow eyes, the mean SFCT of BRVO eyes and fellow eyes were 317.78±24.09μm and 255.21 ±20.40μm, respectively (Fig 2D, p<0.001,paired *t* test). Moreover, the SFCT of BRVO eyes reduced to 287.65±24.42μm rapidly after IVR injection (Fig 2E, p<0.001, paired *t* test).

As was shown in Figure 1 and Figure 2, the SFCT in CRVO eyes and BRVO eyes showed a similar change trend, the thicker SFCT restored after IVR injection. In further, we compared SFCT and SFCT change between CRVO eyes and BRVO eyes. Unexpectedly, although the SFCT of CRVO eyes (326.03μm) was slightly thicker than that of BRVO eyes (317.78μm) at the onset, no significant difference was found between them (Fig 3 A, p >0.05, independent *t* test). The SFCT reduction after treatment were 31.88μm in CRVO eyes and 30.13μm in BRVO eyes, respectively. There was also no statistically significant difference in SFCT reduction between these two groups. (Fig 3 B, C, p>0.05, independent *t* test).

Discussion

The present study showed that the SFCT in eyes with ME secondary to RVO (including CRVO and BRVO) was significantly thicker than that in unaffected fellow eyes, and decreased rapidly within a short term in

response to a single IVR injection, indicating that subfoveal choroid may be involved in the progress of ME secondary to RVO. The SFCT reduction after IVR was mainly caused by ranibizumab, which could permeate the retinal layer and extend to the choroid [27]. Furthermore, the SFCT and SFCT change were compared between CRVO group and BRVO group, no statistically significant difference was found, indicating that SFCT didn't have correlation with RVO subtype.

Macular choroidal thickness was correlated with disease severity and prognosis, EDI-OCT could provide a noninvasive method to evaluate the choroidal thickness in vivo [28, 29]. Over the past several years, many studies had investigated the SFCT in macular-involved diseases. It was reported that the eyes with idiopathic macular hole[30] and dry AMD[31] had reduced SFCT, whereas the eyes with central serous chorioretinopathy (CSC) [32]and Vogt- Koyanagi-Harada (VKH)[33] had increased SFCT. ME is mainly caused by diabetic retinopathy and RVO. Previous studies showed that the SFCT in diabetic macular edema was thinner than that in normal eye [34], and was significantly correlated with the disease severity[35, 36]. With respect to ME secondary to RVO, there had been several studies to investigate choroidal thickness and the role of choroid in RVO eyes. As was mentioned above, Tsuiki and Coban Karatas found that the macular choroidal thickness in RVO eyes was thicker than that in unaffected fellow eyes [12, 13, 28]. In contrast, Du KF and colleagues reported that no significant difference was found between RVO eyes and its fellow eyes [11]. One of the explanation for the conflicting result is the difference RVO phase, the subjects recruited by Tsuiki and Coban Karatas were at acute phase, while the study conducted by Du KF included the patients at longstanding and acute phase, the discrepancy between these studies may be contributed to the patients at longstanding phase. In our study, we collected the resent-onset and treatment-naïve patients, who were at acute phase, and our results were consistent with Tsuiki's findings. Furthermore, several studies demonstrated that choroidal thickness in RVO eyes decreased significantly following anti-VEGF treatment[12, 13, 16, 37], however, Park Jongyeop and colleagues reported that no SFCT change was found after anti-VEGF treatment[9]. The possible cause of this conflicting result might be the different follow-up period. Park Jongyeop evaluated SFCT after 12 months of treatment, while other studies evaluated it within a short follow-up period (ranged 1 month to 6 months). Our study evaluated SFCT after 2 weeks of IVR injection, which was a much shorter follow-up period. Our study still yield the similar finding with the studies which evaluated SFCT in the short term. The hypothesis is that SFCT may decrease in the short term after anti-VEGF treatment, and may restore in the long term. However, further investigation is needed to demonstrate it.

The initial choroidal thickness can be served as a biomarker of disease severity and a predictor of prognosis [35, 36, 38, 39]. Although there were several studies to evaluate the choroidal thickness in RVO, they focused on CRVO or BRVO separately [40, 41]. It had been demonstrated that CRVO eyes had higher ischemic index and VEGF level compared with BRVO eyes. Moreover, increased VEGF would induce vascular hyperpermeability and dilated vessel in choroid layer, which is the main cause of increased choroidal thickness [42, 43]. Thus, it is supposed that the higher the VEGF level is, the thicker the choroidal thickness become. Therefore, we speculated that the SFCT of CRVO eyes might be thicker than that of

BRVO eyes. However, our findings didn't show statistically significant difference between CRVO and BRVO. The possible reasons may be as follows：(1)The patients we collected were ischemic subtype, VEGF level in both CRVO and BRVO eyes was very high; (2)The sample size in each group was too small to detect a significant difference; (3)Besides VEGF, other unknown factors might contribute to choroidal thickness change. Overall, the exact relationship between choroidal thickness and RVO severity require further investigation in the future study.

The present study had several limitations. First, the small sample size, short follow-up period and retrospectively designed study are the drawbacks. The prospective study with large number of subjects and long term follow-up is required in the future. Second, we only collected the patients with ME secondary to ischemic RVO, the patients included are not representative of the population of CRVO and BRVO, they only represent a small population of RVO patients who have the ME complication, this could be a selection bias. In order to further determine the exact relationship between SFCT and disease severity, the patients with non-ischemic RVO, the patients without ME and the patients with other complications (such as neovascularization and glaucoma) should be included in the future study. Third, choroidal thickness can present diurnal variation, the SFCT value is correlated with the measurement time, however, the EDI-OCT for all subjects was not performed within the same range in the study, this could be a possible bias. Fourth, a few subjects with diabetes had been included, although they did not have any sign of diabetic retinopathy according to comprehensive ophthalmic examinations, a potential bias might occur.

Conclusion

In conclusion, in recent-onset and treatment- naïve patients with ME secondary to RVO, the SFCT in affected eyes was statistically thicker than that in its unaffected contralateral eyes, and restored rapidly after 2 weeks of a single IVR injection. Our study may help to elucidate the conflicting results about the SFCT and SFCT change after anti-VEGF therapy. In further, our findings showed that there was no significant difference in SFCT and SFCT reduction between CRVO eyes and BRVO eyes, further study is still needed to investigate the exact relationship between SFCT and RVO severity.

List Of Abbreviations

SFCT Subfoveal Choroidal Thickness

IVR Intravitreal Ranibizumab

RVO Retinal Vein Occlusion

CRVO Central Retinal Vein Occlusion

BRVO Branch Retinal Vein Occlusion

VEGF Vascular Endothelial Growth Factor

AMD Age-Related Degeneration

PCV Polypoidal Choroidal Vasculopathy

CSC Central Serous Chorioretinopathy

EDI-OCT Enhanced Depth Imaging Optical Coherence Tomography

Declarations

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Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FT and FX performed the measurements. ML and QC were involved in planning and supervised the work. FT, HBZ and XZ processed the experimental data, performed the analysis, drafted the manuscript and designed the figures. MLL, KY, and CLS performed the ophthalmic examinations. HH, JL and SMZ collected the demographic characteristics and the choroidal thickness. All authors discussed the results and commented on the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region. The subjects had been informed written consent on the study.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Table 1

Table 1. The patients' demographic characteristics

	CRVO (n=19)	BRVO (n=17)	P
Age, years (Mean ± SD)	57.37±9.75	56.53±8.04	NS*
Gender, Male (%)	12（63.16%）	10（58.82%）	NS**
Axial length, mm (Mean ± SD)	23.55±1.06	23.92±1.03	NS*
Ever smoker (n, %)	6(31.58%)	8(47.06%)	NS**
Systemic diseases			NS**
Hypertension (n, %)	11(57.89%)	8(47.06%)	NS**
Diabetes (n, %)	3(15.79%)	4(23.53%)	NS**
Abnormal coagulation (n, %)	4(21.05%)	3(17.65%)	NS**
BCVA(EDTRS letters)	48.2±19.4	50.2±11.3	NS*
IOP(mmHg)	14.2±2.5	15.4±3.0	NS*

*= Independent *t* test; **= Chi-square test.

Figures

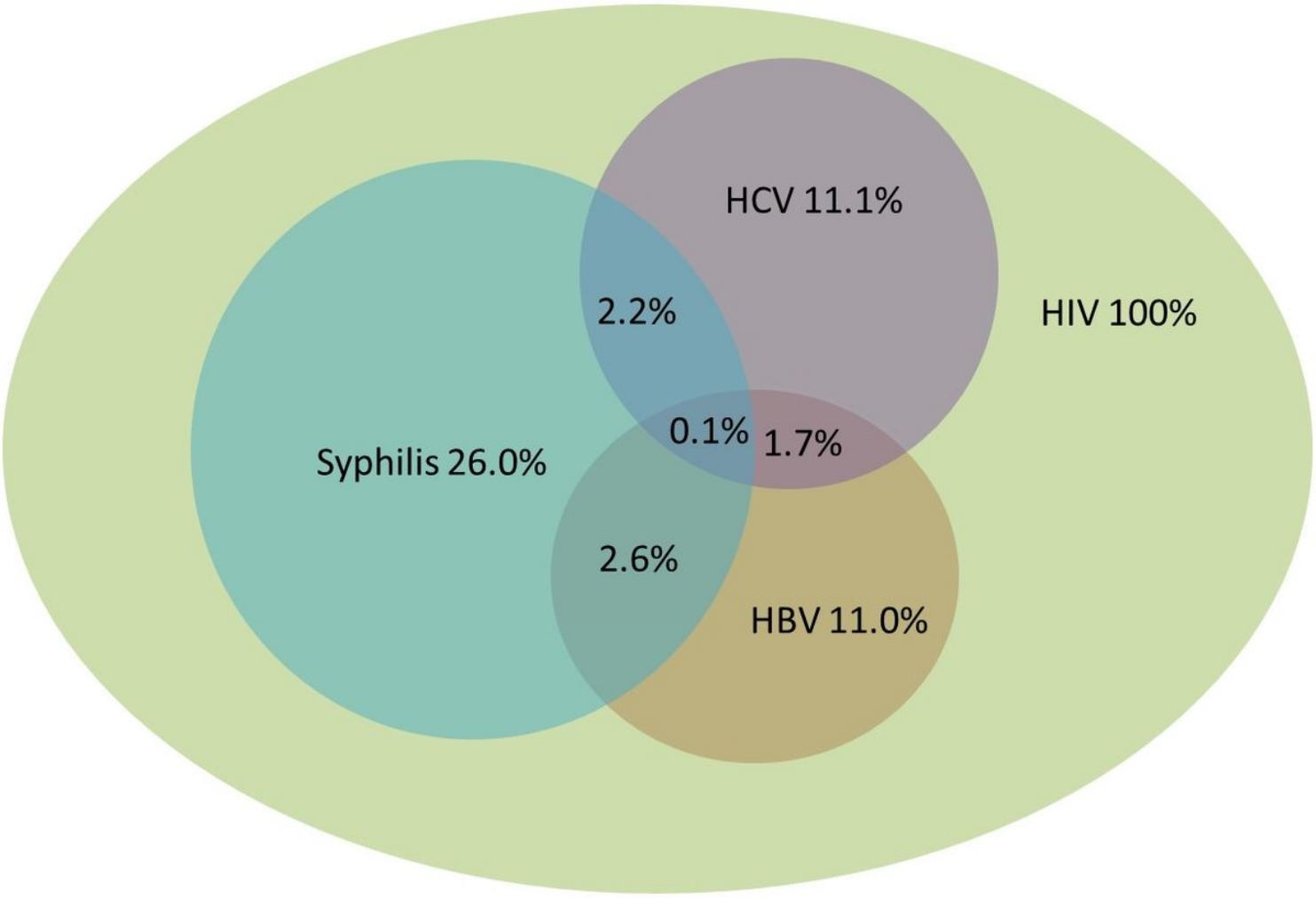

Figure 1

Prevalence of co-infection with HBV, HCV, and syphilis in 1018 HIV-infected patients

Supplementary Files

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