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OCCURRENCE OF HEPATITIS B, HEPATITIS C AND TREPONEMAL CO-INFECTION IN PEOPLE LIVING WITH HIV

Microbiology

Dr Bhagyashree Karekar	Junior Resident.
Ms. Urbi Goswami	IIIrd Year MBBS Student.
Dr Suvarna Joshi	Associate Professor.
Dr Meghna Palewar	Associate Professor.
Dr Sae Pol	Associate Professor.
Dr Rajesh Karyakarte*	Professor and Head of Department, Department of Microbiology. *Corresponding Author

ABSTRACT

Morbidity and mortality of HIV positive patients depends on their response to antiretroviral therapy. Early detection and treatment of co-infection may lead to better outcome as indicated by immune restoration. The present cross- sectional study was undertaken to assess occurrence of co-infections of HBV, HCV and Syphilis and its impact on immune response in HIV positive patients. A total of 200 HIV positive patients receiving ART at the centre of SGH Pune were randomly selected for this study. Blood sample which is routinely collected for CD4 count was taken for our study. No extra sample was taken. This group comprised of 102 male 97 female and one transgender. The age group included in the study was 3years to 76years. A total of 25.5% (51/200) of the patients were tested positive for co-infections. 60.78% (31/51) were positive for Hepatitis B, 3.92% (2/51) for Hepatitis C, 35.29% (18/51) for Syphilis. To study the effect of co-infection on immune response, patient's periodic CD4 count data was analyzed. CD4 count ranged from 15 to 4329 with mean of 392 while in the 51 co-infected patients CD4 count ranged from 3 to 1044 (mean 354). A significant difference in CD4 count was observed between the non-co-infected and co-infected groups. A constantly decrementing trend of CD4 count was the cardinal finding in patients with underlying co-infection.

KEYWORDS

HIV, Hepatitis B, Hepatitis C, Syphilis

INTRODUCTION

Sexually transmitted infections (STIs) are important health related issues both globally as well as in India(1). In India, approximately 6% of the adult population suffers from STIs. HIV, syphilis, hepatitis B virus (HBV) and hepatitis C virus (HCV) are four common infections associated with systemic manifestations and grave consequences that share common routes of transmission, the most common being sexual route(1). Underlying co-infection in PLHIV has a synergistic impact on the pathophysiological manifestation of the individual diseases and their associated sequelae.

In case of syphilis co-infection, there is facilitation of HIV transmission caused by genital ulceration and inflammation(2). On the other hand, HIV/AIDS patients with syphilis have not only decreased CD4+ T lymphocytes but also increased plasma HIV RNA(3). Impaired humoral and cellular immunity depend on the strength of HIV infection and host defence against T. pallidum, leading to change in the clinical aspects and natural course of syphilis, increased number and syphilis lesion infectiousness, and shortened incubation time(3). HIV infections are able to accelerate the process of hepatitis B and hepatitis C, leading to faster development to fibrosis and cirrhosis[4], as well as make liver disease one of the most important non-AIDS (non-acquired immune deficiency syndrome) causes of death in HIV-infected individuals in the past few years[5]. Early diagnosis and treatment of such co-infections can help to reduce the load of HIV related complications on the healthcare system.

AIM & OBJECTIVES :

1) To analyze the occurrence of hepatitis and syphilis co-infection in People Living with HIV(PLHIV).
2) To assess the effect of co-infection on T-cell response of patients enrolling into ART and elicit the aetiology behind lack of response to treatment.

MATERIALS AND METHODS :

A cross-sectional study was conducted with 200 HIV positive blood samples of all age groups irrespective of gender. Blood sample which is routinely collected for CD4 count was taken for our study. This group comprised 102 male 97 female and one transgender.The age group included in the study was 3 years to 76 years. The specimens were subjected to Treponema Pallidum Haemagglutination Assay (TPHA) (PLASMATEC KIT) and Rapid Plasma Reagin (RPR) (OMEGA DIAGNOSTICS) tests using standard and reverse algorithm.

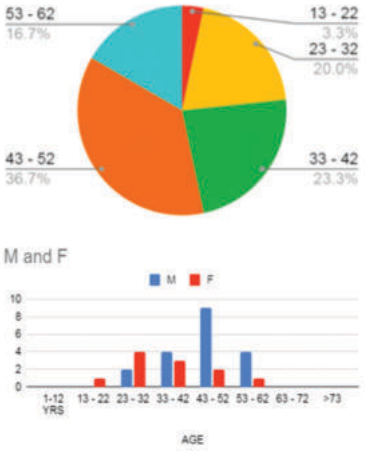
A hepatitis panel using Rapid Immunochromatography testing kit(BIOLAB DIAGNOSTICS) was performed on the samples to check for hepatitis coinfection. CD4 counts and viral load values were collected for the entire population enrolled in the study from the hospital ART Centre and NACO website databases, to monitor their response to ART treatment and disease progression. PLHIV patients who have been counseled and are started on antiretroviral treatment, and had given their consent were enrolled in the study. Variables taken under study assessment were- age, gender, CD4 count, viral load, HBsAg and HCV panel results,TPHA and RPR results, type of ART the patient is started on, duration and compliance to treatment with regular follow ups present or not.

RESULTS:

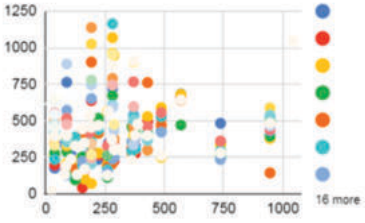
A total of 15.5% (31/200) patients were tested positive for co-infection with Hepatitis B and 1% (2/200) for Hepatitis C.One patient each with Hepatitis B & Hepatitis C co-infection were excluded because they were transferred to another center. Although the data for one patient with Hepatitis C coinfection is available we will not be commenting on it to minimize incidence prevalence bias. To study the effect of co-infection on immune response, the CD4 Count of the patients with and without co-infection were analyzed in juxtaposition. A CD4 count of <500 cells/cmm (poor prognosis) in patients with HBV co-infection was significant($p=0.034$) compared to non-co-infected patients($p=0.06$). Among the 30 patients tested positive for HBV, the majority being chronically HIV infected patients 61.30% (19/30); 20 were men (64.5%) and 11 were women (35.48%). One had both Syphilis and hepatitis B coinfection. The two patients tested positive for HCV were both males from the age group 20-40 years.

According to the WHO clinical staging for people diagnosed with HIV, 17 were classified under WHO stage I; 9 patients under WHO stage II; 3 under WHO Stage II and 1 under Stage IV. No variation was found in

treatment given with respect to WHO staging of patients.



Age wise gender distribution in Hepatitis coinfected patients



Cd4 count range and variation of hepatitis B co-infection patients

Table 1: Treatment Regimen for hepatitis B co-infection patients

HEPATITIS		
Start of ART	ART Regimen	No. of patients
2007 - 2011	TLE	1
	Initially ZLN now TLD in 2021	2
	TLD	1
	ZLN	1
2012 - 2016	TLE	7
	ZLN	3
	TL+ATV/r	1
2017 - 2021	Initially TLE shifted to TLD	2
	TLE	12
	TLD	3

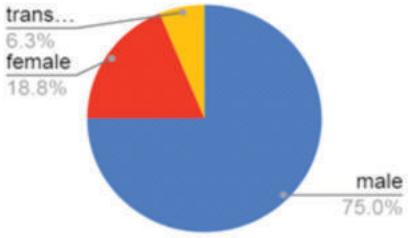
A total of 9% (18/200) patients were found to have exposure to T. pallidum. To study the effect of the co-infection on immune response, data of CD4 count was analyzed. Two patients were excluded from the study as they were transferred to another centre. Baseline CD4 count ranged from 3 to 4329 with mean of 392 in 200 patients while in the 16 co-infected patients CD4 count ranged from 3 to 815 (mean 287). Out of the 16 patients who were infected with syphilis, 12 were male, 3 were female and 1 was transgender. Age group of syphilis infected patients ranged from 23 to 74 years.

Out of the 16 patients who were tested positive for syphilis, 12 patients were positive for TPHA and RPR. Four were TPHA positive and RPR negative. RPR positivity was found in 1:2 titre in 5 patients, 1:4 titre in 3 patients, 1:8 titre in 1 patient, 1:32 titre in 1 patient and 1:64 titre in 2 patients.

Table 2 : Treatment regimen of HIV Patients with syphilis Co-infection

SYPHILIS		
Start of ART	ART Regimen	No. Of Patients
2007 - 2011	ZLE (1),	1
	TLE (1)	1
2012 - 2016	TLD (1)	1
	TLE (1)	1
	ZLE (1)	1
2017 - 2021	TLE (1)	1
	ZLE (1)	1
	TLD (9)	9

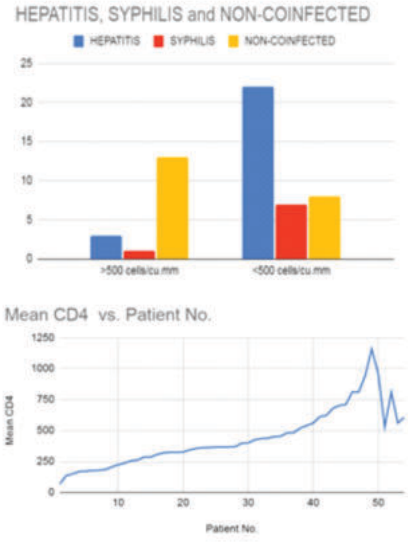
Cd4 count of <500 cells / mm3 was observed in 87.5% (14/16) of the patients. Nine of them were newly diagnosed patients (in 2021) while 7 were previously diagnosed. The viral load of the 7 patients who were chronically infected was found to be TND i.e. target not detected'. The viral load testing of the remaining nine patients who were newly diagnosed was not done as they had not completed six months of antiretroviral treatment.[6] However most of them had a CD4 count < 350 cells /mm3. They all were started on Cotrimoxazole Preventive Therapy (CPT).(7) CD4 count of <500 cells / mm3 observed in 87.5% (14/16) of the patients.



Gender wise distribution of syphilis co-infection patients

According to the WHO clinical staging for people diagnosed with HIV, 12 were classified under WHO stage I while 4 patients under WHO stage II. It was seen that the treatment regimen did not differ according to the clinical staging.

For all 200 patients the latest CD4 count was available. However there were only 54 patients for whom data for periodic CD4 count was available. Amongst them 37 of them had a CD4 count of < 500 cells / mm3 whereas 17 of them had a CD4 count > 500 cells / mm3 . A total of 29/37 (78.37%) patients were suffering from coinfection. Hepatitis B coinfection was seen in 22/29 (75.86%) whereas 7/29 (24.13%) were suffering from treponemal infection. Only 8 patients who were not suffering from HBV and/or syphilis coinfection had a CD4 count of < 500 cells / mm^3 .



Charts showing mean CD4 count distribution among the 54 patients

VIRAL LOAD TESTING:

Detectable levels of viral load was available for 28 patients. However the sequential testing reports were not available probably due to the lockdown during the COVID19 pandemic.Out of them 9 were coinfected with HBV and/or syphilis. In 8 patients an increase in viral copies in 2018 was observed. However they responded to antiretroviral therapy and the viral load was below the detection limit.. This showed that they responded to the ongoing antiretroviral treatment. Similar finding was observed in one patient suffering from syphilis coinfection.

DISCUSSION

HIV continues to be a major global public health issue, having claimed 36.3 million [27.2–47.8 million] lives so far .[6]There were an estimated

37.7 million [30.2–45.1 million] people living with HIV at the end of 2020, over two thirds of whom (25.4 million) are in the WHO African Region.[6] Chronic hepatitis B virus (HBV) infection affects 5– 20% of the 36 million people living with HIV worldwide, and hepatitis C virus (HCV) affects 5- 15%, rising to 90 % among people who inject drugs[8]. HIV infection has a significant impact on the natural history of chronic HBV infection, with increased levels of HBV DNA, accelerated progression of liver disease and increased liver-associated mortality compared to HBV mono-infection[9]. Previously studies which have evaluated age as a variable have not found any significant association and trends in age related occurrence. In this study, we found an increasing occurrence of co-infection in PLHIV patients in higher age groups. This result can be attributed to the chronicity of infection with HIV.

When the patients were divided into groups according to gender, the male to female ratio of occurrence of co-infection increased with a ratio of 2:1.From a biological point of view, women are more susceptible to HIV infection than men and on the contrary the occurrence of HBV mono-infection with a poorer prognosis of transformation to Hepatocellular Carcinoma(HCC) is more common in males than females[10]. Studies show that Male to female transmission of STIs is between two to four times more efficient and as most sexually transmitted infections (STIs) are asymptomatic in women, diagnosis and treatment is more difficult. Women also have limited access or receive an inferior quality of care than men and frequently wait longer than men before visiting health facilities.[12]
Studies have shown that a higher frequency of HBsAg loss has been associated with lower CD4+ T cell count prior to initiation of HBV-active ART and a greater increase in CD4+ T-cells following ART[9] which is contrary to the results obtained in our study wherein 80.66%(p=0.034) of the co-infected patients had a CD4 count of <500cells/mm^3 compared to the 66.67%(p=0.06) of the non-coinfected patients indicative of poorer prognosis in co-infection despite active treatment.

In the setting of co-infection with Hepatitis B Virus (HBV), the availability of ART, with activity against both HIV and HBV, particularly tenofovir, has led to significant improvements in outcomes(9).When the treatment plan of the 31 co-infected patients was compared with the duration of infection and periodic trends of CD4 count, we observed that majority of the older patients were enrolled under TLE Regimen, newer patients were started on TLD as per the new WHO Guidelines. 11 patients had a decreasing trend in CD4 Count despite which they didn't have a change in the treatment plan. Of the 18 patients enrolled in TLE previously 9 showed improvement in CD4 count which justifies the treatment plan and doesn't call for prompt change. Ancillary treatment for Hepatitis B infection other than Tenofovir, can lead to better improvement in CD4 counts of patients.

Syphilis is not only a frequently detected sexually transmitted disease in developing countries but also has an increasing importance for HIV infected individuals as it leads to rapid progression.[13] Hence, the early diagnosis of syphilis is of paramount importance for HIV-infected patients.[13] Because syphilis and HIV can be asymptomatic, many individuals are unaware of their infection and remain undiagnosed. [10] Majority of the patients had CD4 count < 500 cells / mm^3 in our study . In a study conducted by Harnati et al syphilis infection in HIV patients was associated with increased viral load and decreased of the CD4+ count.[10] Studies have proven that increase of viral load occurs mainly in patients with secondary syphilis infection and also those who are not adherent to ART.[7]

However in our study, 7 patients who were probably suffering from a past infection of syphilis were on ART. Although viral load of these 7 patients was below the detection limit , significant immunological improvement was not seen in terms of CD4 count. The data of viral load for the newly diagnosed patients was not available as they had not completed six months of antiretroviral treatment.[14]

When the patients were divided into groups according to gender, the male to female ratio in occurrence of co-infection was found to be 3:1. In a previous study of 830 HIV patients by Signorini et al it was also proved that male to female occurrence of HIV-syphilis coinfection to be 4:1.[11] In the same study they also concluded that age was not a significant factor in determining the prevalence of syphilis co-infection.[11] In our study also age did not play a significant role.

One female patient was a case of latent syphilis and had completed the treatment of benzathine penicillin for the same. As she was initially enrolled under Obstetrics for a Caesarean section, her testing was routinely done for syphilis as per the antenatal care protocol. Therefore she was diagnosed and treated for the treponemal infection. She was newly diagnosed of HIV infection and was on TLD regimen. The data for the treatment of syphilis coinfection in other patients was not available with the ART center in the hospital. So there is a high possibility that PLHIV with syphilis coinfection are going undiagnosed.

CONCLUSIONS

The purpose of this study was to investigate the occurrence and trends of syphilis and hepatitis co-infection in PLHIV. It is evident from the results obtained, that co-infection has a marked negative impact on CD4 count despite treatment. The study highlights the importance of diagnosing coinfection so as to improve immune response and reduce morbidity. Because of the overlap in risk behaviors that lead to HIV, syphilis and hepatitis infections, integrated public health efforts are needed to prevent new coinfections, and to improve the quality of life of the patient.

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