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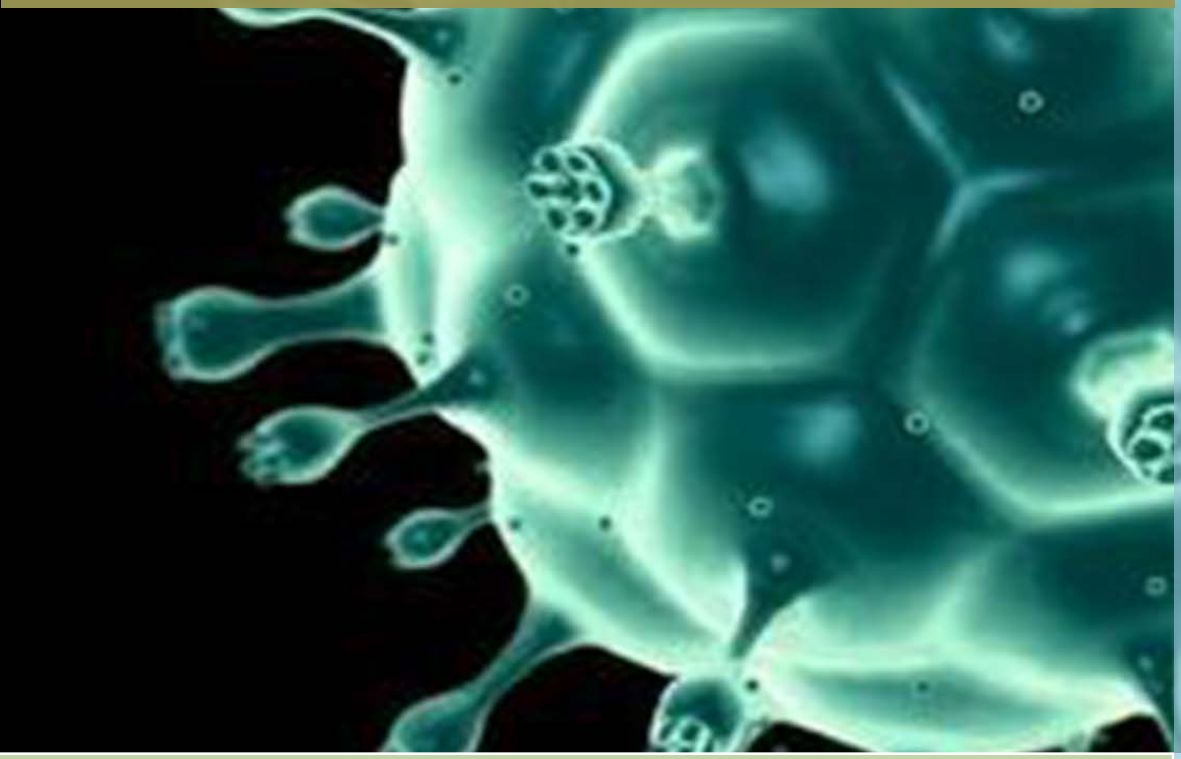

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Editorial

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HIV/AIDS and African American Women: Research Opportunities to Stem the Epidemic

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BACKGROUND

HIV/AIDS in communities of color across the United States continues to be a devastating epidemic. The Centers for Disease Control (CDC) estimates the rate of new HIV infections to be higher among African American women compared to Whites and other races. In 2009 for example, African American women made up only 14% of the US. Female population and yet accounted for 66% of new HIV cases among all women. In 2010, African American women experienced the disease at a rate that was 20 times higher than White women, and 5 times higher than Hispanic women (CDC, 2012a). This data points to the need for further research to stem the spread of the disease in communities that are already adversely affected by HIV/AIDS.

HIV rates in New Jersey are similar to that of the nation's. While African Americans make up 14% of the state's total population, they account for 54% of all people diagnosed with HIV/AIDS. Among those living with HIV/AIDS in New Jersey, African American women made up 64% of HIV/AIDS cases. Of the 64%, injection drug abusers accounted for 38% of the HIV/AIDS infections, while 55% were the result of heterosexual exposure.

This editorial will highlight the ongoing research that is being conducted to stem the spread of HIV/AIDS in communities of color and specifically among African American women.

PROJECT DASH

Divas Against the Spread of HIV/AIDS

A study on HIV risk and Mental Health among African American Adolescent Girls with HIV+ Mothers is a study which utilizes a mixed method research approach to explore the relationship and communication characteristics between daughters and their HIV+ mothers, as predictors of sexual behaviours and HIV risk of the adolescent. The objective of this project is 1) to explore the experiences of HIV positive minority women in New Jersey in accessing and navigating the healthcare system with a view to addressing them and 2) to examine the relationship and communication characteristics between daughters and their HIV+ mothers around HIV prevention.

A mixed-methods approach (quantitative and qualitative) was used to obtain data from study participants. Quantitative data was obtained using surveys while qualitative data were obtained using face-to-face one-on-one interviews. The total number of participants was (n=74) who completed demographic surveys (n=51 mothers, 23 daughters) and a subset of mothers and daughters who additionally completed in-depth interviews (n=15 mothers, 15 daughters). Among mothers, 98% of respondents were African American, 73% had been HIV-infected for at least 10 years, and the mean age was 49.9 years. Among daughters, 85% reported having a good relationship with their mother where they felt comfortable talking to her about sex.

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Findings from Project DASH study have the potential to guide the development of a larger study to: 1) examine specific elements of the mother-daughter relationship, that can protect daughters against HIV risk, 2) identify modifiable risk factors for HIV/AIDS in adolescents, 3) develop interventions that target mother-daughter sexual communication as a methodology to reduce HIV risk. The proposed approach has tremendous potential to further examine specific drivers of HIV/AIDS in urban communities. The ultimate goals is decreased transmission to further prevent the spread of HIV in African American adolescent females.

CONCLUSION

Drawing on available evidence from existing literature, the research study outlined above demonstrate promising data that places the life experiences of women within a socio-ecological framework; one that considers the various ways in which cultural norms and preferences, individual needs, disparities in the access of neighborhood resources, and psychological distress intersect to affect a woman's overall potential and ability to manage the multiple complications associated with HIV and its related comorbidities.

The findings suggest that comprehensive services that not only include culturally sensitive education components, but also strengthen and facilitate an individual's existing personal, social, and environmental support networks are needed to improve health outcomes among African American women living with HIV.

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Case Report

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Cerebral Toxoplasmosis in a Treatment Naive HIV Patient with High CD4 Count Responding to Treatment with a Regime of Cotrimoxazole and Pyrimethamine: Do We Need to Start Prophylaxis for Toxoplasmosis at a Higher CD4 Count?

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ABSTRACT

Cerebral toxoplasmosis is one of the commonest opportunistic infection of the nervous system in HIV patients. We present a case of gradual onset haemiparesis in an ART naïve HIV patient with high CD4 count who was subsequently diagnosed to be a case of cerebral toxoplasmosis based on radiological and serological investigations. The patient responded to a regime of Cotrimoxazole and Pyrimethamine. His CD4 count at diagnosis was 299/µl. HAART was started after completion of treatment of cerebral toxoplasmosis. Prophylaxis against toxoplasmosis is recommended with cotrimoxazole if the CD4 count is below 200/µl. However, in this case as the patient had developed toxoplasmosis at a CD4 count value above the cut-off value for prophylaxis for cerebral toxoplasmosis, it may be worth considering to starting prophylaxis at a higher CD4 count than 200/µl and continuing for a longer time than the current guidelines.

KEYWORDS: Cerebral toxoplasmosis; Opportunistic infections; HAART; Cotrimoxazole.

ABBREVIATIONS: HAART: Highly Active Antiretroviral Therapy; IgG: Immunoglobulin G; ELISA: Enzyme-linked immunosorbent assay.

INTRODUCTION

Opportunistic infections are often the presenting diagnosis in patients with HIV/AIDS. Though most of the opportunistic infections occur at low CD4 counts, we present a case of cerebral toxoplasmosis presenting with progressive hemiparesis, who was subsequently diagnosed to have HIV infection with a CD4 count of 299/µl and made good recovery with a regime comprising of pyrimethamine, sulfadoxime and cotrimoxazole. The case is of interest as cerebral toxoplasmosis has been rarely reported with high CD4 count in treatment naïve HIV patients. The completeness of recovery with commonly available drugs before the initiation of Highly Active Antiretroviral Therapy (HAART), thereby makes a case for initiation of prophylaxis with cotrimoxazole for toxoplasmosis at higher CD4 count in HIV infected patients.

CASE HISTORY

A 47 year old trucker was admitted with history of progressive weakness of right half of the body with headache that started about four weeks back. The patient had become non-

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ambulatory a week before the admission and was unable to feed or clothe himself on his own. His speech had become slurred. He had history of contact with multiple sexual partners. Examination revealed a male patient of BMI 23.5 kg/m^2 with normal blood pressure and pulse rate. He was conscious with Grade 3 upper motor neuron type of weakness of both upper and lower limbs on right side along with dysarthria. Early papilledema was seen on both eyes on examination.

CT scan of head - both plain and contrast enhanced, showed multiple ring enhancing lesions on both sides of brain with surrounding cerebral edema. He tested positive for HIV 1. Subsequent MRI of brain showed multiple target lesions on both sides of the brain. The CD4 count of the patient was 299/µl. Blood examination of the patient showed mild normocytic, normochromic anemia with normal biochemical parameters. He tested negative for Hepatitis B and C. Chest X-ray and ultrasound examination of abdomen did not reveal any pathology. He tested positive for IgG anti toxoplasma antibody (Figure 1).

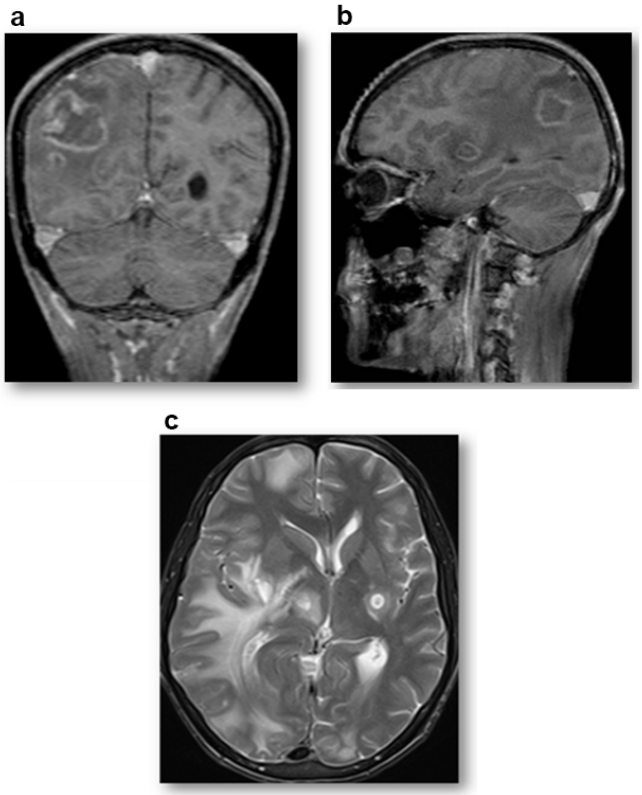

Figure 1: a) MRI showing cerebral toxoplasmosis on right frontoparietal region – sagittal section. b) MRI T1 image (coronal section) showing multiple lesions. c) T2 weighted image showing cerebral toxoplasmosis.

A diagnosis of Stage IV HIV infection with toxoplasma encephalitis was made. The patient was initiated on a regime of pyrimethamine 200 mg and sulfadoxime 4 gm (Day 1) in two divided doses followed by pyrimethamine 50 mg and sulfadoxime 1 gm and cotrimoxazole double strength – 2 tabs thrice daily from Day 2. Inj. dexamethasone 8 mg IV thrice daily was started for cerebral edema. Folic acid supplementation was also given.

The patient responded to treatment and by the end of 2nd week was able to walk with support. Follow-up CT scan of head showed resolution of the lesion by 3rd week. The dose of dexamethasone was gradually tapered and the patient was continued on cotrimoxazole double strength tablets with pyrimethamine and sulfadoxime for a total four weeks of therapy. HAART was started 2 weeks after completion of treatment of toxoplasma encephalitis.

DISCUSSION

Cerebral toxoplasmosis is a major cause of morbidity and mortality among HIV-infected patients, particularly from developing countries.[1] Cerebral toxoplasmosis is an HIV-indicative event in 35% of patients and an AIDS-defining event in 75% of cases.[2] Globally, *T. gondii* causes the most common focal brain lesion in HIV-infected patients.[3] In most of the studies, incidence of toxoplasma encephalitis have been reported with CD4 count of less than 100 cells/µl.[4] In a study involving 97 HIV patients with toxoplasma encephalitis, the median CD4 count was 68 cells/µl.[5] Similar findings have been observed in studies from Puerto Rico and Brazil where toxoplasma encephalitis was observed in patients with low CD4 count.[6,7] The incidence of toxoplasmosis varies by country and depends on the prevalence of *T. gondii* infection in the general population. *T. gondii* has an unusual clonal population structure consisting of three widespread lineages known as I, II, and III. Differences in genotypes of *T. gondii* isolates, races and ethnicities and the mode of transmission also seem to influence the occurrence of the infection.[8]

Cerebral toxoplasmosis causes unifocal or, more commonly, multifocal lesions and, less frequently, diffuse encephalitis. Patients usually present with subacute symptoms. The clinical manifestations depend on the location and number of lesions. More frequent complaints include: headache (49-63%), fever (41-68%), focal deficits (22-80%), seizures (19-29%), mental confusion (15-52%), ataxia (15-25%), lethargy (12-44%), cranial nerve palsies (12-19%) and visual alterations (8-15%). Other manifestations include dysarthria, cognitive dysfunction, raised intracranial pressure and involuntary movements. The definitive diagnosis of cerebral toxoplasmosis requires the presence of the tachyzoite form of the parasite in cerebral tissue to be directly demonstrated by brain biopsy. In clinical practice, presumptive cerebral toxoplasmosis diagnosis depends on an association of serological, clinical and radiological findings.[9] Detection of Immunoglobulin G (IgG) is possible within 2 weeks of infection using the Enzyme-linked immunosorbent assay (ELISA) test.

Diagnosis is confirmed with a response to empiric anti-*Toxoplasma* therapy. A favorable clinical and radiological response is expected within 10-14 days of specific treatment.[10]

The treatment of *T.gondii* infection is usually by a combination of pyrimethamine, sulfadiazine and leucovorin though

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alternative regimes include pyrimethamine plus clindamycin, cotrimoxazole and atovaquone plus pyrimethamine.[11] Three randomized double-blinded trials of cerebral toxoplasmosis treatment have been published comparing pyrimethamine plus sulfadiazine with pyrimethamine plus clindamycin[12] and pyrimethamine plus sulfadiazine with cotrimoxazole.[13] In a review of these studies The Cochrane Collaboration did not identify any superior regimen among these three combinations for cerebral toxoplasmosis treatment.[14] With sulfadiazine being not available widely, cotrimoxazole has been used in treatment of Toxoplasmosis. Cotrimoxazole has been used as an alternative treatment for toxoplasma encephalitis because it is inexpensive, well-tolerated, and as effective as pyrimethamine-sulfadiazine, which is the first-line drug regimen. The drug has been found effective (85.5%) with a relatively low incidence of side effects (22%; 7.4% requiring treatment interruption). Relapses did occur in some patients and the risk factors for relapse was poor treatment and/or prophylaxis adherence.[15] The safety of cotrimoxazole has also been established in treatment of congenital toxoplasmosis which is one of the most common causes of fetal death.[16]

HIV Patients with CD4 count <100 cells/µl are given prophylaxis against *T.gondii* with a single double-strength-tablet daily dose of cotrimoxazole and continued till CD4 count >200/µL for more than 6 months.[17] However, in a recent study, *T.gondii* cases have been reported in patients with high CD4 count >200/µl with 299 cases Per Year Follow up (PYFUP)[18] with more than 50 cases reported at CD4 count >500/µl PYFU. Toxoplasma encephalitis has also been reported in patients with CD4 count >300 cells/µl but these patients had a history of CD4 count of <100 cells/µl at one stage and the rise of CD4 count was attributed to HAART. These cases of toxoplasma encephalitis occurring with of high CD4 count have been attributed to persistence of immune dysfunction in spite of HAART[19,20] or poor compliance. As toxoplasma encephalitis responds well to cotrimoxazole, it may be worth considering starting prophylaxis for toxoplasmosis at higher CD4 count (>200/µl) that may be continued till CD4 count remains well over 200/µl for a longer period.

CONCLUSION

Cerebral toxoplasmosis has been rarely been reported in treatment naïve HIV patients with CD4 count >200 µl. As cerebral toxoplasmosis respond well to a combination of cotrimoxazole and pyrimethamine in a HIV patient, it may be worth considering to start prophylaxis against toxoplasmosis with cotrimoxazole at a CD4 count higher than 200/µl as cases of toxoplasmosis have been reported with higher CD4 count.

CONFLICTS OF INTEREST: None.

CONSENT

The patient has provided written permission for this publication.

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Research

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Prevalence of Hepatitis B Virus among Blood Donors and Assessment of Blood Donor's Knowledge about HBV in Sudan

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ABSTRACT

The prevalence of Hepatitis B varies between different regions of Sudan according to several published reports, but no data is available about the prevalence of HBV in all Sudan states, in a given time. The objective of this study was to determine the seroprevalence of hepatitis B virus among blood donors in all Sudan states in the years 2012-2014, its also assess the knowledge of blood donors about HBV modes of transmission, complications and preventive measures. A total of 200 blood donors presenting to the central blood bank were interviewed to assess their knowledge together with collection of retrospective data from monthly reports delivered to the central bank from regional blood banks to calculate the prevalence of HBV in the contributing States. The study revealed poor knowledge about HBV transmission and its consequences and the degree of knowledge was not related to the level of education. The majority of study population was not vaccinated, mainly due to lack of awareness about hepatitis B vaccine.

The study also included the prevalence of HBV in all Sudan states in 2012-2014. In 2012, the prevalence ranged between 0.1% in Northern State and Nahr Alnile to 15.7% in South Kordofan. In 2013, the prevalence ranged between 0% in Northern State to 12.3% in the White Nile State. In 2014, it was between 0.5% in Northern State to 8.8% in Al-Gadarif state. It concluded that despite the difference in prevalence between the states and the difference of prevalence in the same state over the years, the overall rates are lower than those previously reported. Poor knowledge about HBV risk factors, complications and preventive measures, was observed in all sectors, even in those with higher level of education. Lack of knowledge is a major obstacle in controlling HBV transmission.

KEYWORDS: Vaccine; Virus; Liver cirrhosis; Hepatitis; Blood bank.

INTRODUCTION

Hepatitis virus infections are the most common cause of liver disease worldwide. Sudan is classified among the countries with high hepatitis B virus seroprevalence Hepatitis B Virus (HBV) infection is a global public health problem. It is estimated that there are more than 350 million HBV carriers in the world, of whom one million die annually from HBV-related liver disease.[1] The implementation of effective vaccination programs in many countries has resulted in a significant decrease in the incidence of acute hepatitis B. Nevertheless, hepatitis B remains an important cause of morbidity and mortality.

Sudan is classified among the countries with high HBV endemicity. Earlier studies

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carried out in the 80's and 90's estimated higher rates of HBsAg of 17.5% among asymptomatic blood donors.[2] The screening of blood donations for HBV was introduced throughout the country in 2002, before which time screening was performed in only a few centers in Khartoum. Vaccination for HBV was included as part of the extended programme of immunization in 2005. The introduction of vaccination and the screening of blood and blood products reduced the rate of HBV infection and the carrier pool.[3] In more recent studies, the HBV seropositivity varies between different regions of Sudan, but ranges between 5 and 7% in the general population.[3-6] More than a decade passed since the introduction of blood screening in blood banks, and this study is to monitor how much this together with other measures including vaccination were effective in reducing the infection rates of HBV. No recent data is available about the prevalence of HBV in all Sudan states, in a given time. The available data are scattered data of some states that included small numbers of patients.

One of the major factors attributing to increased transmission of HBV is the lack of awareness about the prevalence, mode of transmission and preventive measures. The study is designed to test the knowledge of blood donors about HBV. The study population were usually young and middle aged males, representing the most productive age group. Infection of this age group with HBV, HCV or HIV, has a major impact on the population as a whole. Knowledge and awareness about the mode of transmission is important for the planning and preventive health education programme. Disease control by preventive strategy is more effective than a curative one.

METHODOLOGY

200 males presenting to the national blood bank for blood donation are approached to participate in this study, after an informed verbal consent for acceptance, a structured questionnaire including age, marital status and level of education is filled. The questionnaire also tests the donor's knowledge about risk factors and mode of transmission and the consequences of HBV infection. Donors were asked if they were vaccinated and whether they are interested to know the results of their viral screening.

Retrospective data regarding the prevalence of HBV in the years 2012, 2013 and 2014 was collected from monthly reports delivered to the central bank of blood services from the Sudan States major blood banks. The number of states included in the study was 15 states in 2012, 17 states in 2013 and 18 states in 2014. Methods for screening for HBsAg differ between states; some states use ICT for testing, others use ELISA, and some states use both methods.

The data was analyzed with statistical package for social sciences (SPSS 11.5). The results were presented in tables, discussed and compared with local and international studies.

RESULTS

200 blood donors were included in this study, to test their knowledge regarding HBV out of which 30% were under the age of 25 years, 49% were between 25-35 years, 19% were between 36-45 years and 2% were above the age of 46 years. Sixty two percent of the donors were single and 38% were married. (Tables 1-3)

State	Total no. of donors tested	No of HBV +ve Donors	Percentage
Khartoum	19450	710	3.65%
Al-Gezira	109588	4851	4.4%
Sinar	7873	159	2%
Kassala	6099	225	3.67%
Red Sea	4602	74	1.6%
A-Gadarif	1850	56	3%
Blue Nile	3125	68	2.17%
White Nile	5162	301	5.83%
Nahr El Nile	4956	8	0.1%
Northern state	2561	5	0.1%
North Kordofan	5409	179	3.3%
South Kordofan	4248	670	15.7%
North Darfor	5331	230	4.3%
South Darfor	4834	124	2.5%
West Darfor	1984	127	6.4%
Total	187072	7787	4.1%

Table 1: Prevalence of HBV among blood donors in fifteen states in 2012.

State	Total no. of donors	No of HBV +ve Donors	Percentage
Khartoum	120850	5680	5.49%
Al-Gezira	13583	746	4.7%
Sinar	12784	407	3.1%
Kassala	7780	447	5.74%
Red Sea	4524	103	2.2%
A-Gadarif	66655	3140	4.71%
Blue Nile	3601	166	4.61%
White Nile	3331	410	12.3%
Nahr El Nile	2232	38	1.7%
Northern state	263	0	0%
North Kordofan	4651	282	6%
South Kordofan	1976	94	4.75%
North Darfor	3157	249	7.88%
South Darfor	8364	502	6%
West Darfor	1741	118	6.77%
East Darfor	1280	65	5%
Middle Darfor	413	24	5.8%
Total	257185	12471	4.8%

Table 2: Prevalence of HBV among blood donors in seventeen States in 2013.

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State	Total no. of donors	No of HBV +ve Donors	Percentage
Khartoum	90905	2505	2.7%
Al-Gezira	27990	1470	5.25%
Sinar	20171	863	4.2%
Kassala	10910	499	4.5%
Red Sea	4214	187	4.4%
A-Gadarif	12042	1063	8.8%
Blue Nile	6178	254	4.1%
White Nile	10970	894	8.14%
Nahr El Nile	5557	53	0.9%
Northern state	4118	22	0.5%
North Kordofan	14222	805	5.6%
South Kordofan	6514	183	2.8%
North Darfor	10417	420	4%
South Darfor	2183	99	4.5%
West Darfor	2019	92	4.5%
East Darfor	2608	95	3.6%
Middle Darfor	3438	208	6%
West Kordofan	27484	1401	5%
Total	261940	11113	4.2%

Table 3: Prevalence of HBV among blood donors in eighteen States in 2014.

Regarding the educational level of the donors 1% were illiterate, 11.5% had a primary school level of education, 4% had an intermediate school education, 29% had a high school education and 54.5% had university level or postgraduate education.

Forty one donors (20.5%) had been in contact with a HBV positive patient, either a relative, neighbour or a friend.

When asked about HBV modes of transmission, 23% knew that HBV can be transmitted through blood, 0.5% mentioned sexual transmission, 8.5% knew that it can be transmitted both sexually and through blood transmission. Only 3% had a good knowledge and mentioned the three major modes of transmission, and the majority (59%) did not know any of HBV modes of transmission. Of those 0.8% were illiterate, 16.9% had a primary school level, 3.4% had a intermediate school level, 29.7% had a high school level, and 49.2% had a university or postgraduate level of education.

When asked about the consequences of HBV infection, 74 donors (37%) knew that HBV can cause liver cirrhosis, seven donors (3.5%) knew that HBV can cause liver cirrhosis, and it can be complicated with portal hypertension and Hepatocellular Carcinoma. But 119 donors (59.5%) were not aware of the consequences of HBV, of those 0.8% were illiterate, 16% had a primary school level, 3.4% had a intermediate school level, 33.6% had a high school level, and 46.2% of donors with a university level of education did not know any of HBV modes of transmission.

Only seventeen donors (8.5%) were vaccinated against HBV, 183(91.5%) were not vaccinated, of them 10(5%) did not think vaccination was important and 173(86.5%) did not know about the vaccine.

One hundred eighty seven (93.5) wanted to know the result of their screening, 13(6.5%) did not want to know, mainly because of the fear of positivity and the impact of a positive result in their lives, jobs and families.

The overall prevalence of HBV in Sudan in 2012 was 4%. The prevalence varies between the 15 states included in the surveillance, ranging between 0.1 in Nahr Alnile and the Northern state to 15.7% in South Kordofan. In 2013, 17 states were included in the survey and the overall prevalence of HBV was found to be 5%. The prevalence of HBV ranged between 0% the Northern state to 12.3% in White Nile state. In 2014 HBV prevalence was found to be 4.2%. The survey included eighteen states and HBV prevalence ranged between 0.5% in the Northern state and 0.9% in Nahr Alnile to 8.8% in Gadarif.

DISCUSSION

Despite the implementation of effective vaccination programs, hepatitis B remains an important cause of morbidity and mortality worldwide. Understanding the epidemiology of the disease is essential in developing programs to prevent and treat this global infection.[1] The lack of knowledge about HBV modes of transmission, its consequences, and its preventive measures is a major cause of increasing prevalence of HBV. Other causes include the influx of immigrants from endemic areas and the improvement in diagnosis and documentation of HBV infection.

All blood donors included in the study are males. Females do not usually donate blood in Sudan. Men of young or middle age are those who willingly donate blood.

Although 20% had a relative, neighbour or a friend diagnosed with HBV or HBV related disease, their knowledge of HBV was generally poor. When asked about HBV modes of transmission; 23% knew that HBV can be transmitted through blood, 8.5% knew that it can be transmitted both sexually and through blood transmission, but only 3% mentioned all three major modes of transmission, including vertical transmission. The majority (59%) did not know any of HBV modes of transmission; of those 49.2% had a university level of education or higher.

Only 3% knew that HBV can cause liver cirrhosis and can be complicated by portal hypertension and Hepatocellular Carcinoma. The majority (59.5%) of the study population of whom 46.2% were university graduates did not know any consequences of HBV infection. The lack of knowledge is observed in all groups irrespective of their education level. A study was carried out among non medical students of the University of Kassala, to assess their knowledge and awareness towards HIV and HBV infection. It revealed that the students had poor knowl-

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edge about HBV mode of transmission, symptoms and preventive measures, in comparison they had better knowledge about HIV infection.[7]

Most of those vaccinated (8.5%) were offered the vaccine by their employers (e.g. Central Sudan bank, Al Gaili petrol refinery). The study population included two doctors who were not vaccinated. The majority (93.5%) wanted to know the result of their viral screening.

In 2012, the Northern and Nahr Alnile states had the lowest prevalence of HBV (0.1%). In 2013 no cases were detected in the Northern Province, probably because of the small size of the population tested, i.e. only 263 donors. The incidence in Nahr Alnile, in the same year, was 1.7%. In 2014, HBV prevalence in the Northern state was 0.5%, and was 0.9% in Nahr Alnile. Our data showed a lower percent when compared to a previous study in 2007, conducted among blood donors in Shendi, Nahr Alnile, and was found to be 5.1%.[8]

The highest prevalence of HBV in 2012 was in South Kordofan, which was 15.7%. In 2013, the White Nile state had the highest percent of 12.3. And in 2014, Al-Gadarif showed the highest prevalence of 8.8%. No published data about the prevalence in these states were found.

The prevalence in Khartoum, in 2012-2014 was 3.6%, 4.7%, and 2.7%. A study conducted, in 2008-2011 on patients undergoing surgery at Alshab Hospital, one of the major hospitals in Khartoum, revealed a higher percentage of 4.9%.[9] In a more recent study in 2012 conducted among 843 health care workers in public teaching hospitals in Khartoum showed that Anti-HB core was found to be 57%, HBsAg was 6%, HBeAg was 9%, and Anti-HBsAg was 37%.[10]

The HBV prevalence in Al-Gezira state (Central Sudan) in 2012-2014, was 4.4%, 5.49%, and 5.2% respectively. These percentages are lower than those observed in a study conducted in 2000, in Um Zukra village in Al-Gezira state, the percent of HBV was found to be 6.9%.[3] An earlier study in 1992, revealed much higher percents, it studied the prevalence of hepatitis B surface antigen in blood donors and laboratory technical staff in Al-Gezira state, and was found to be 17.3%, and 12.1% respectively.[11] A study of the epidemiology of HBV in Al-Gezira State in 1989 reported a high HBsAg rate of 18.7% and anti-HBc of 63.9%.[12]

The prevalence of HBV in South Darfor (West Sudan) in 2012-2014 was 2.5%, 6% and 4.5% respectively. An earlier study in 2007 conducted in blood donors in Nyala (West Sudan) revealed a percent of 6.25%.[5]

The prevalence of HBV in Kassla (East Sudan) in 2012-2014 was 3.6%, 5.7% and 4.2 % respectively. A much higher percentage of 8.2% was found in a study conducted in 2011 on healthy visitors at Kassala Hospital.[13]

The prevalence in the Red Sea state in 2012-2014 was 1.6%, 2.2%, and 4.4% respectively. In a study in 1987, HBsAg was detected in 14% of sexually active heterosexuals in Port Sudan and Suakin, and 27% were positive for Anti-HBc.[11]

Poor knowledge about HBV risk factors, complication and preventive measures, was observed in all sectors, even in those with higher level of education. It is attributed to the absence of formal school based health education. Lack of knowledge is a major obstacle in controlling HBV transmission.

With the exception of the Northern and Nahr Alnile States that sustained low levels of HBV infection throughout the years, there is a large variation in the prevalence of HBV among different states, together with differences in prevalence in the same state throughout the years. This is due to the influx of immigrants from the borders of Sudan, and the internal population movements between states. But generally the rates are lower than those previously reported,[3-6] as the overall prevalence in Sudan in 2012-2014 was 4.1%, 5% and 4%, respectively.

CONCLUSION

Although there is a large variation in the prevalence of HBV among the states, together with differences of prevalence in the same state throughout the years, the rates are generally lower than those previously reported. The overall prevalence in Sudan in 2012-2014 was 4.1%, 5% and 4% respectively.

The highest prevalence of HBV in 2012-2014 was in South Kordofan, the White Nile, and Al-Gadarif respectively. From 2012-2014, the Northern and Nahr Alnile states had the lowest prevalence of HBV. More measures should be taken by health authorities, especially in the states with a high prevalence of HBV, including mass screening and vaccination programmes. Despite the availability of HBV vaccine, almost all the donors were not vaccinated, poor knowledge about HBV mode of transmission, symptoms and preventive measures was demonstrated in all sectors irrespective of their level of education. HBV transmission, and thus prevalence can be controlled by improving the population knowledge.

As a conclusion, more efforts are needed to increase awareness about HBV infection, and ways of preventing transmission. Knowledge can be delivered through media, poster and brochures targeting all sectors, but focusing mainly on the young population as they in turn can act as a source of knowledge to their families. Blood donors found to be seronegative for HBV, should be advised to receive HBV vaccine and mass vaccination through large companies should be encouraged. And finally further wide population prospective studies are needed including both males and female of all age groups, to assess the prevalence of HBV and the risk factors implemented.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONSENT

We obtained a written consent from all the 200 blood donors included in the study, it includes information and agreement that the data will be published.

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HIV/AIDS RESEARCH AND TREATMENT

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Review

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Why Novel Nanoparticle-based Delivery Platforms Hold Key for HIV/AIDS Treatment and Prevention?

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KEYWORDS: Nanoparticle; Regimens; Nanotechnology; nanoART.

ABBREVIATIONS: HAART: Highly active antiretroviral therapy; nanoART: nanoformulated ART; ATV: Atazanavir; FA: Folic Acid; RTV: Ritonavir; MDM: Monocyte-derived macrophage; P407: Poloxamer 407; RNAi: RNA interference; RISC: RNA Induced Silencing Complex; CNTs: Carbon nanotubes; SWNTs: Single-walled nanotubes; SPIONS: Super paramagnetic iron oxide nanoparticles; DCs: Dendritic Cells; APCs: Antigen-Presenting Cells; MHCs: Major Histocompatibity Complex; LC: Langerhans Cells; CTL: Cytotoxic T-lymphocyte.

INTRODUCTION

The administration of highly active antiretroviral therapy (HAART) to HIV/AIDS patients has greatly reduced their morbidity and mortality. However, HAART regimens have myriad of limitations, which make it difficult to completely eradicate HIV/AIDS from the body. Cells harboring latent HIV reside in restricted areas in the body: cellular and anatomical reservoirs. The residing of HIV in these restricted sanctuaries makes HAART regimens incapable of completely eliminating HIV from the body. In addition, HAART regimens have to be taken for a lifetime making AIDS patients develop resistance to the drugs. When HIV/AIDS patients take HAART regimens overtime, the drugs result in side effects, such as drug toxicities and treatment fatigue. The development of nanotechnology has revolutionized medicine today. Nanotechnology have the potential to mitigate the challenges that doctors and scientists are facing with the current treatment and prevention of HIV/AIDS. In this review, I discuss the challenges of HAART regimens and how the novel nanoparticle-based delivery platforms can be advanced for HIV/AIDS treatment and prevention.

NANOTECHNOLOGY-BASED PLATFORMS FOR SYSTEMIC DELIVERY OF ANTIRETROVIRAL DRUGS

Complete eradication of HIV from the body with current HIV regimens is becoming a nightmare to scientists. Memory CD4+ T cells and macrophages act as latent reservoirs for HIV with the later serving as a host for viral genetic recombination producing an elusive mutant viral genotypes.[1-4] In addition, cells harboring latent HIV reside in restricted parts of the body. These cells are highly concentrated in specific anatomical sites: secondary lymphoid tissues, testes, liver, kidney, lungs, gut and CNS.[3-5] Taking the current HIV regimens overtime result in side effects that are detrimental to HIV/AIDS patients: drug toxicity, treatment fatigue, drug-drug interaction.[6]

Novel nanoparticle-based delivery systems are key in eradicating the virus from reservoirs. They are, therefore, effective in HIV prevention and treatment. Nanotechnology is a scientific discipline that involves fabricating materials at molecular level. Nanotechnology is the study of structures with approximately 1-100 nm in size in at least one dimension. However,

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the applications of nanotechnology also consider structures up to several hundreds of nanometers.[4,7]

Nanotechnology-based platforms have revolutionized medicine regarding treatment of various diseases. In the recent past, the application of nanomedicine for treatment and prevention of HIV and AIDS has gained much attention. The current novel nanoparticle-based delivery systems have been used not only to boost conventional treatments of HIV/AIDS; they have also been use to advance therapeutic strategies: gene therapy, immunotherapy and vaccine developments.[4]

There are several advantages of nanotechnology-based platforms for systemic delivery of ART as compared to conventional methods. Nanotechnology-based platforms improve adherence to the drugs by keeping the circulation of drugs at therapeutic concentrations for longer durations. Their small size enhances and modulates the distribution of hydrophobic and hydrophilic drugs in tissues because of their large surface to volume ratio.[4] Targeted delivery of nanocarriers to CD4 cells and macrophages and to other organs ensures that the ART reach latent reservoirs.[4] The nanocarriers have properties that improve drug delivery: increased drug stability, enhance intestinal absorption and bioavailability, prolonged pharmacokinetics, optimized drug bio-distribution, improved toxicity profiles, and selective drug delivery.[5,8-10]

In what follows, I describe the recent nanotechnology-based novel platforms for systemic delivery of antiretroviral drugs. Drug polymer conjugates have been used to deliver ART because: they increase stability, reduce toxicity and enhance long circulation duration and can permeate across physiological barriers due to their small size.[8] Drug polymer conjugates are used to deliver nucleoside reverse transcriptase inhibitor. Nano-sized monophosphate-polymer conjugate delivery system investigated by Yang, et al. was made using stavudine (d4T). In this nanoparticle, Phosphoramide linkage was used to conjugate d4T to chitosan to yield chitosan-*O*-isopropyl-5′-O-d4T monophosphate conjugate. This conjugate was found to enhance the activity of ART and had low toxicity compared to native nucleoside d4T.[8]

Another nanocarrier used to deliver ART is Poloxamer 407-coated nanocrystals, a nanoformulated ART (nanoART). A nanoART facilitates drug delivery within intracellular compartments and within the sites of viral replication cycle as investigated by Dongwei Guo, et al. Poloxamer 407-coated nanocrystals containing a protease inhibitor Atazanavir (ATV) easily accumulated in macrophages. The concentrations of nanoATV were found to be approximately higher in cells compared to those that could be achieved by the native drug.[11] From this experiment, it can be deduced that the nanocarrier enhances the retention of drugs in subcellular compartments as compared to the native drug.

Biocompatible polymers such as NanoART used as nanocarrier in nanomedicine to deliver ART can be improved by coating it with Folic Acid (FA) to increase drug targeting and retention of drug in the cell. It has been reported that biocompatible polymers, such as Poloxamer 407 (P407) and poloxamer 188 (P188) covalently linked to FA to encapsulate known hydrophobic ART – atazanavir (ATV) and Ritonavir (RTV) increases the retention capacity of the drug and slow the dissociation of drug inside human Monocyte-derived macrophage (MDM) carrier.[12] Coating nanoART with FA particle not only improves intracellular drug targeting; it also improves pharmacokinetics and pharmacodynamics of the drug. Pharmacodynamics of long-acting folic acid-receptor targeted ritonavir-boosted atazanavir nanoformulations.[12-14]

ALTERNATIVE APPROACHES FOR HIV/AIDS TREATMENT

Due to elusive nature of HIV, its eradication from the human body is becoming a herculean task to scientists. However, there are alternative approaches that have been developed in the recent past to eradicate HIV, such as gene therapy, nano-immunotherapy and vaccinology.

NEW NANOTECHNOLOGY PLATFORMS USED IN GENE THERAPY FOR HIV/AIDS

Gene therapy is the direct transfer of genetic material to cells or tissues to treat acquired diseases, such as AIDS and inherited disorders. Once a gene is inserted into a cell infected by HIV-1, it interferes with the viral infection and replication. Viral vectors are being used for delivering agents and various clinical trials are in progress.[15,16] However, it has been found that using viral vectors for gene delivery have a lot of limitations: toxicity, immunogenicity, insertion mutagenesis and scale-up procedures.[4,17,18]

RNA interference (RNAi) holds some promise for therapeutic potential for HIV/AIDS[15,19] RNAi contributes to gene silencing. When a double stranded RNA is introduced into an appropriate cell, it is cleaved by an enzyme called Dicer into 21 base pair nucleotides to produce double stranded siRNA.[6] These siRNAs are incorporated into RNA Induced Silencing Complex (RISC). The single-stranded RNAs in the RISC guide the cleavage of mRNAs that contains sequences complimentary to the single-stranded RNAs in the RISC leading to gene silencing.[6]

The siRNA has been implicated in interfering with HIV-1 by degrading mRNA.[6] The siRNA interferes with viral replication cycle by blocking the translation and transcription of viral genes and by doing so prevents the production of proteins and genomic RNA. The siRNA can also inhibits the entry and fusion of the virus by interfering with production of cell receptors or co-receptors such as CD4, CCR5, and/or CXCR4, which are responsible for viral entry.

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To realize the potential of RNAi, there has to be sufficient technique to deliver it to targeted tissues. The emergence of new nanoparticle-based delivery systems has contributed immensely to efficient and safe delivery of RNAi. The use of inorganic nanoparticles, such as Carbon nanotubes (CNTs) is preferable in gene delivery because: they have good storage ability and are not susceptible to microbial attack. Also, they can easily cross the plasma membrane using endocytosis without causing cell death due to their nanometer needle structure.[16,20-22]

One such nanoparticle-based delivery system to deliver RNAi is Single-walled nanotubes (SWNTs). SWNTs have been used to deliver C×CR$_4$ and CD$_4$-specific siRNA to human T cells in HIV infections.[23] Low biocompatibility and solubility in aqueous solution of SWNTs can be improved by surface modifications or functionalization.[24] Aside from SWNTs, Super paramagnetic iron oxide nanoparticles (SPIONS) have been shown to be excellent carrier for delivering siRNA to cells because of their biocompatibility and target functionalized.[23]

NANOIMMUNOTHERAPY FOR HIV/AIDS TREATMENT

Unlike gene therapy and ART that target HIV, immunotherapy modulates the immune response against HIV.[4] Hence, immunotherapy is aimed at restoring the regular function of the immune system as a therapeutic approach against HIV/AIDS.[25] In this regard, strategies to reconstitute the immune function seem to be a promising approach to eradicate HIV/AIDS. Immunotherapy involves the use of immunomodulatory agents such as cytokines or antigens to modulate the immune response to restore cellular and humoral immunity in HIV-infected patients.[4] The development of cellular and humoral immunity requires the presence of Antigen-Presenting Cells (APCs), such as Dendritic Cells (DCs). The DCs are very instrumental in activating and functioning of both innate and adaptive immunity.[26]

The DCs initiates cellular and humoral immunity by processing and presenting the antigens on their surface through Major Histocompatibity Complex (MHCs) to CD4$^+$ and CD8$^+$ T cells. Since the delivery of immunogenic factors through viral vectors targeting DCs have various risks, the development of polymeric systems to deliver immunogenic factors targeting DCs is showing potential for immunotherapy.[4]

A new developed platform for nanomedicine for immunotherapy is DermaVir patch, which is on its phase II clinical trials.[27] DermaVir consists of an HIV-1 antigen-encoding plasmid DNA that is chemically formulated in a nanoparticle. DermaVir patch got its name from where it is administered. It is administered under a patch after a skin preparation that aids the nanoparticle delivery to Langerhans Cells (LC). The LC mature into dendritic cells when transiting and transporting the nanomedicine to draining lymph nodes. The dendritic cells eventually process and present the DNA-encoded antigens to naïve T-cells that induce the cellular immunity.

NANOPARTICLE-BASED DELIVERY SYSTEMS FOR HIV/AIDS VACCINES

The development of HIV/AIDS vaccine has been confronted with a plethora of challenges: diversity of viral strain and sequence, the evasion of cellular and humoral immunity responses by the virus and lack of methods to elicit neutralizing antibodies and cytotoxic T cells that are broadly reactive.[28]

To generate effective immunity, both humoral and cellular immunity have to be elicited. For cellular immunity, the antigens have to be processed and presented in form of peptides by the APCs, such as DCs to T cells. The MHC class I present intracellular antigens to CD8$^+$ cells and MHC class II presents extracellular antigens to CD4$^+$ cells.[29]

Nanoparticle-based delivery platforms for vaccines have several advantages over conventional vaccines. There is controlled release of antigens that could lead to the prolonged and stronger initiation of the immune response. The encapsulation of the antigen by the nanoparticle protects the antigen from the body fluid thereby increasing the half-life of the immunizing antigen.[4] The surface of the nanoparticle can be functionalized to target antigen delivery to DCs to effectively deliver antigens and initiate an immune response.[4] Nanoparticle can be designed to elicit both cellular and humoral immunity. For instance, nanoparticle can be designed to present the antigen to DCs by encapsulating antigens eliciting cellular immunity or directly present the antigen directly to B cells to elicit humoral immunity by functionalizing the surface of the nanoparticle to absorb the antigen.[35] Unlike conventional vaccines that are limited to one route of administration, that is, intramuscularly, nanoparticles can be administered through oral, dermal, vaginal and nasal routes where mucosal immunity could be induced.[30]

The p24-PLA nanoparticles has been successfully used to elicit both humoral and cellular immunity. HIV antigen p24 was loaded into surfactant-free anionic poly (dl-lactic acid) (PLA) and subsequently injected into the rabbits, mice and macaques. The p24-PLA nanoparticles elicited very high antibody titers and strong Cytotoxic T-lymphocyte (CTL) responses in mice, rabbits and macaques as compared to soluble antigen.[31] The p24-PLA nanoparticles can be used to induce maturation of DCs to enhance cellular immunity. For instance, incubating DCs and p24 antigen adsorbed in PLA nanoparticles was capable of inducing the maturation of dendritic cells. This enhanced the maturation of cell surface markers, such as MHC classes I and II, CD40, CD80 and CD86 as well as the production of cytokines, such as IL-4 and IL-7.[32]

CONCLUSION AND FUTURE PERSPECTIVES

While the nanoparticle-based delivery platforms have been advanced for HIV/AIDS treatment and prevention, there are certain limitations that need to be addressed to realize the po-

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tential of nanomedicine. Some of the nanoparticles administered may not reach their targeted tissues because of their premature degradation. For instance, some of the nanoparticles administered orally are degraded in the gut or are unable to penetrate the gut compromising their absorption.[22] In some cases, the body may respond by getting rid of some of the nanoparticles administered through phagocytosis and other mechanisms[33] compromising their targeted functions. Nanoparticles may not only generate adverse immunological responses, they may also accumulate in the body leading to toxicity.[34] The immunological responses and toxicity may have adverse effects to the HIV/AIDS patients. There is no data on metabolic processing of nanoparticles. Therefore, there is dire need of much research in nanotoxicology.[23] Scaling up in nanotechnology is much expensive. Optimization is much simpler at a laboratory scale as compared to industrial level.[35]

Therefore, more work needs to be done in the field of nanotechnology to make nanocarrier therapeutic approach feasible and to translate nanotechnology from lab to clinical settings. Nanotechnology should offer significant cost to benefit ratio to gain wide acceptability.[4] There is a need to use better surface modifiers for nanocarriers for improved targeting and longer duration and action of drug. Since use of combination of drugs have been found to be more effective in eradicating HIV, studies should be conducted in nanocarriers for combined delivery strategies. In addition, much research should be done on toxicity of nanocarriers.[36] Generally, nanoparticle based delivery platforms have contributed a great deal in advancing HIV/AIDS treatment and prevention. They have improved drug delivery in many ways: they have improved adherence to the drugs increasing their stability, their targeted delivery achieve more efficient distribution, they have reduced drug toxicity levels significantly and they provide a means of permeating blood brain barrier.

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HIV/AIDS RESEARCH AND TREATMENT

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Brief Research Report

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Development of the M184V Mutation in HIV-1 Infection and Subsequent Treatment Outcomes

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ABSTRACT

Objective: The purpose of this study was to describe the occurrence of the M184V mutation in a single clinic setting over a period of 10 years. We examined the combination Antiretroviral Therapy (cART) being taken at the time of first identification of the M184V mutation as well as Second Line Regimens (SLR) started immediately after the documentation of M184V. SLR were evaluated for frequency and time to Virologic Suppression (VS) as well as frequency and time to subsequent Virologic Failure (VF).

Design: This was a retrospective cohort study of all Human Immunodeficiency Virus (HIV)-infected patients receiving care at the Washington University School of Medicine Infectious Disease Clinic in St. Louis, MO, USA between January 2001 and June 2010.

Methods: Prevalence of the M184V mutation, ART regimen leading to M184V acquisition, and outcomes of SLR in patients with M184V (as measured by time to initial VS and subsequent VF on SLR) were analyzed in a retrospective cohort study of all HIV-infected persons receiving care at a university clinic.

Results: Of 2500 screened clinic patients, 220 had an acquired MI184V mutation (8.8%). There were 158(72%) male and 171(78%) African-American patients. The mean time from the start of a regimen to the documented M184V mutation was 575(0-3253) days. Independent of Nucleoside Reverse Transcriptase Inhibitor (NRTI) backbone, the mean time to development of M184V in Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) (n=109) and Protease Inhibitor (PI) based (n=84) regimens was 538(+/- 556) and 622 (+/- 620) days, respectively (p=0.325) approximately, 78% of patients achieved VS on a SLR in a mean of 179 days. Of the 122(57%) of patients whose SLR retained FTC/3TC, VS was achieved in 80% compared to 74% without FTC/3TC (p=0.285) with no significant difference in time to VS (152(+/- 187) and 181(+/- 257) days respectively, p=0.406). There were no significant differences in achievement of VS in PI (n=158) and NNRTI (n=27) – based SLRs independent of the NRTI backbone, 76% *vs.* 78%, respectively (p=0.837) with a similar time to VS (180(+/- 228) *vs.* 128(+/- 158) days, p=0.313). All patients on PI+Raltegravir (RAL) (n=10) and PI+NNRTI (n=12) – based regimens achieved VS (*vs.* 76% in PI+2NRTI (p=0.078 and p=0.054, respectively). Regardless of SLR, about 50% of each group experienced VF after VS with a similar time to failure.

Conclusions: M184V mutation developed in 9% of patients in a mean of 575 days with no significant differences between ART regimens. Following initiation of an SLR, the majority of patients achieved VS in approximately 179 days irrespective of the regimen. The addition of 3TC/FTC did not significantly affect VS. Although numbers were small, 100% of patients on two fully active non-NRTI-backbone-based regimens attained VS. Approximately half of all patients subsequently failed on SLR, regardless of regimen used, suggesting that the development of M184V is a marker of noncompliance to therapy.

KEYWORDS: HIV; Drug resistance; Lamivudine; Antiretroviral therapy; HIV drug resistance.

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ABBREVIATIONS: VS: Virologic Suppression; SLR: Second Line Regimens; cART: combination Antiretroviral therapy; VF: Virologic Failure; NRTI: Nucleoside Reverse Transcriptase Inhibitors; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; FTC: Emtricitabine; 3TC: Lamivudine; RAL: Raltegravir; PI: Protease Inhibitor.

INTRODUCTION

Combination active antiretroviral therapy (cART), consisting of 3 antiretroviral drugs from 2 or 3 classes, has reduced morbidity and mortality due to HIV-1 infection since its introduction. Current guidelines for the treatment of HIV in naïve patients consists of 2 Nucleoside Reverse Transcriptase Inhibitors (NRTIs), plus either a Non-NRTI (NNRTI) or ritonavir boosted Protease Inhibitor (PI) or integrase inhibitor.[1] Due to its tolerability, relative ease of administration, and availability in fixed combination products, either lamivudine (3TC) or the related drug emtricitabine (FTC) are a part of all recommended initial cART regimens, and are commonly included in second line regimens (SLR) after virologic failure (VF).[1] However, lamivudine and emtricitabine have relatively low barriers to the development of virologic resistance, most commonly through the emergence of a single mutation in the reverse transcriptase gene, M184V.[2] Emergence of drug resistance is associated with increased mortality in patients who receive first-line cART.[3] An estimated 5% of patients on cART develop genotypic resistance after 1 year, 10% after 2 years, and almost 30% develop virologic failure (VF) with at least 1 major mutation within 6 years of starting cART.[3,4] Although the most common mutations are to NNRTIs, which develop in approximately 50% of failing regimens, resistance to 3TC and FTC *via* the single resistance mutation, M184V, occurs in 35% of failing regimens.[3-5] This mutation impairs the fitness of the virus, and therefore discontinuation of 3TC/FTC in a regimen results in apparent reversion to wild type genotype, although the mutation remains archived, and will re-emerge once 3TC/FTC are restarted. Currently there are no guidelines directing second line therapy after developing the M184V mutation. Previous studies have demonstrated that continuing to maintain FTC or 3TC in the backbone of the second line regimen (SLR) has similar activity to using regimens with at least 2 other active NRTIs;[6,7] several studies suggest that SLR with protease inhibitors (PI) may be more effective.[8,9] Several reports have suggested that failure of second line therapy after developing M184V is due more to non-adherence, and not primarily to virologic failure (VF),[7,10] and that even the initial failing regimen may be used if adherence is improved. The purpose of this study was to describe the occurrence of the M184V mutation in a single clinic setting over a period of 10 years; to examine second line therapy choices, regarding VS, time to VS, and VF following virologic suppression (VS).

MATERIALS AND METHODS

This was a retrospective cohort study of all HIV-infected patients receiving care at the Washington University School of Medicine Infectious Disease Clinic in St. Louis, MO, USA between January 2001 and June 2010. Prevalence of the M184V mutation, outcomes of antiretroviral therapy in patients with M184V, as measured by time to virologic suppression (VS) and failure were analyzed. VS was defined as HIV viral load <400 copies/mL after initiation of SLR. VF was defined as VL>400 either after a period of VS or persistent HIV VL>400 for 6 months on a second line regimen (SLR). Differences between the groups were compared using χ^2 and Fisher exact test for categorical data and Mann-Whitney tests for continuous variables; statistical significance was defined as $P<0.05$. The study was approved by Washington University School of Medicine Human Research Protection Office.

RESULTS

Of 2500 screened clinic patients, 220 were identified as having acquired M184V mutation (9%). Similar to the clinic population as a whole, 158(72%) patients were male and 171(78%) were African-Americans. HIV was acquired predominantly through sex, with 124 men reporting sex with men and 85 reporting only heterosexual encounters. Nine patients were injection drug users. Concurrent resistance to other antiretrovirals was common, with 172 patients having other NRTI resistance, 136 with genotypic NNRTI resistance, and 35 with PI resistance. The mean time from the start of a regimen to the documented M184V mutation was 575(0-3253) days. There was a significant difference in the time to development of M184V when 3TC was used (mean 706 days, SD 673 days) compared to FTC (mean 394 days, SD 304 days) (p=0.002) (Figure 1). Despite changing cART prescribing patterns over time, no significant differences were seen in the time to develop M184V between different NRTI backbone partners to 3TC or FTC (other NRTIs used included zidovudine (AZT), tenofovir (TDF), abacavir (ABC), didanosine (ddI), stavudine (d4T)), and no significant differences were seen between NNRTI or PI based regimens. The mean time to development of M184V in NNRTI (n=109) and PI-based (n=84) regimens was 538(±556) and 622(±620) days, respectively (p=0.325).

Following initiation of an SLR, approximately 78% of all study patients (n=171) achieved VS in a mean of 179 days. Of the 122(57%) patients whose SLR retained FTC/3TC, VS was achieved in 80% compared to 74% without FTC/3TC (p=0.285) with no significant difference in mean time to VS (152(±187) and 181(±257) days respectively, p=0.406). About 50% of these groups experienced VF after VS with a similar time to failure (273(±188) days *vs.* 221(±156) days) (p=1).

There were no significant differences in achievement of VS in PI (n=158) and NNRTI (n=27) – based SLRs independent of the NRTI backbone, 76% *vs.* 78%, respectively (p=0.837) with a similar mean time to VS (180(±228) *vs.* 128(±158) days, p=0.313). However, all patients with two non-NRTI class agents in the regimen (PI+raltegravir (n=10) or PI+NNRTI (n=12)) achieved VS (*vs.* 76% in PI+2NRTI (p=0.078 and p=0.054, re-

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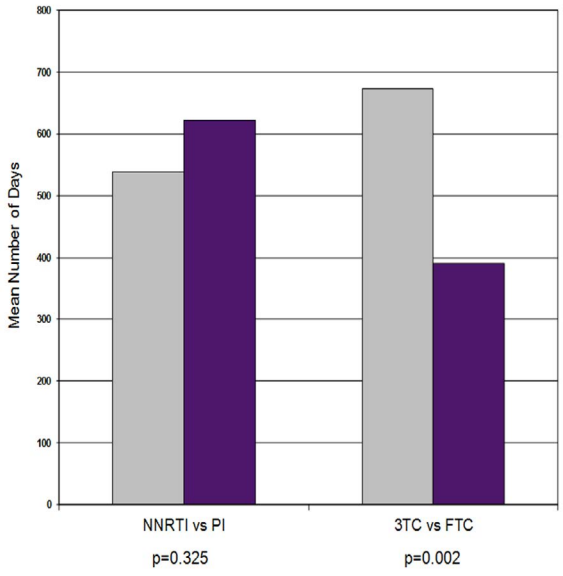
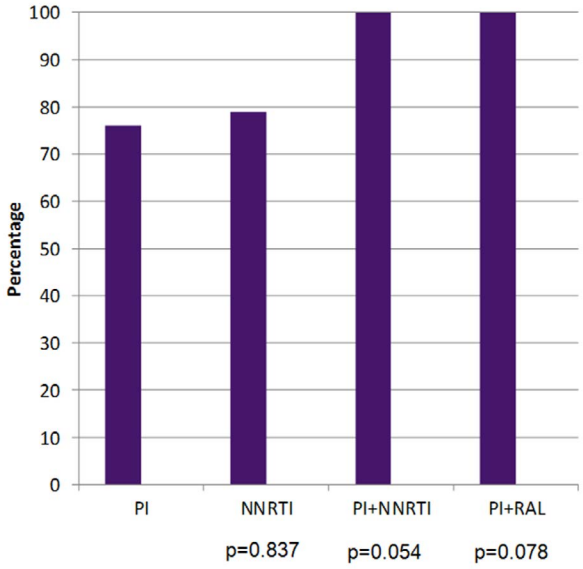


PI: Protease Inhibitor; NNRTI: Non nucleoside Reverse Transcriptase Inhibitor; 3TC: Lamivudine; FTC: Emtricitabine.

Figure 1: Time to the development of the M184V mutation.



PI: Protease Inhibitor; NNRTI: Non nucleoside Reverse Transcriptase Inhibitor; RAL: Raltegravir

Figure 2: Virologic suppression (VS) with second-line regimens (SLRs).

spectively) (Figure 2).

Of the 171 subjects that achieved virologic suppression on SLR, 84 subsequently failed and 87 maintained suppression. There were no differences in the regimens which maintained virological success *versus* those that that met the definition of virological failure. Fifty percent of the patients on PI-based SLRs met virologic failure compared to 52% of patients on NNRTI-based regimens, 51% on PI+RAL, and 42% on PI+NNRTI. Of the SLR regimens which failed, 22 had further Reverse Transcriptase (RT) resistance mutations, and 16 had further protease resistance mutations.

DISCUSSION

Despite its early development as an antiviral, lamivudine, and its related drug emtricitabine, are among the most successful and well-tolerated antiviral agents used in cART. Resistance to these NRTI *via* the M184V mutation impairs viral fitness, but is extremely common. Despite this, all currently recommended regimens for treatment-naïve patients include either 3TC or FTC. A review of the literature does not reveal guidelines, consensus, or much data recommending second-line regimens after the development of the M184V mutation.

We examined the development and consequences of the M184V mutation in patients seen in the Washington University Infectious Disease Clinic. Of the approximately 2500 unique patients seen from 2001-2010, the M184V mutation developed in 9% in a mean of 575 days with no significant differences between cART regimens. A difference was seen between 3TC and FTC in the development of M184V, which is potentially due to the different pharmacokinetics of the two agents, with FTC being more forgiving of intermittent adherence.[11] However, this difference might also be due to shifts in other antiretrovirals given concurrently, as regimens containing 3TC (and especially the use of the combination pill combivir or AZT/3TC) tended to occur on average between 2003-2004, while regimens containing FTC (and especially the combination pill Truvada, or TDF/FTC) tended to occur between 2007-2008. Following initiation of a SLR, the majority of patients achieved VS in approximately 179 days irrespective of the regimen. There was no significant benefit to the addition of 3TC/FTC as it did not significantly affect VS. Although numbers were small, 100% of patients on regimens containing two active agents in classes other than NRTIs (i.e. PI+NNRTI or PI+RAL) were virologically suppressed. The patients may or may not have been on a single active NRTI. This may be due to increased potency of these regimens, although studies of NRTI sparing regimens have not been proven to be better than NRTI containing regimens in naïve patients.[12-14] It is possible that the use of additional drugs is beneficial in the setting of NRTI resistance. Alternatively, the additional pill burden may have induced higher rates of adherence, at least upon initiation of the regimen.

Although the data presented in this study is observational, the fact that no significant differences were seen between PI-based or NNRTI-based regimens, together with only an 80% success rate in obtaining virologic suppression, a subsequent 50% failure rate of maintaining virologic suppression, and low levels of further resistance mutations, suggests that failure of the SLR is likely due to subsequent non-adherence. As it has been shown in other studies, our data suggest that the appearance of the M184V mutation warrants further discussion and emphasis on strict adherence to the second line regimen regardless of how it is structured. Although, numbers were small, 100% of patients

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on a fully active regimen containing two agents which are not in the NRTI class were virologically suppressed, suggesting that NRTI- sparing regimens may be preferable after the M184V mutation and other NRTI resistance mutations develop.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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DISCLOSURE

The study was approved by Washington University School of Medicine Human Research Protection Office.

CONSENT

Our application for waiver of informed consent/authorization was approved by The Washington University Human Research Protection Office.

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