HIV-2 Infection: Where Are We Today?

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ABSTRACT

Context: The choice of antiretroviral therapy for HIV-2 differs from that for HIV-1, underscoring the importance of differentiating between the two. **Aims:** The current study was planned to find out the prevalence of HIV-2 infection at our center and to find out the utility of the current diagnostic algorithm in identifying the type of HIV infection. **Setting and Design:** Retrospective analysis in a tertiary care teaching institute over a period of three years. **Materials and Methods:** All patients diagnosed as HIV infected using NACO/WHO HIV testing strategy III were included in the study. They were classified as HIV-1 infected, HIV-2 infected and HIV-1 and HIV-2 co-infected based on their test results. For discordant samples, immunoblotting result from National Reference Laboratory was considered as final. **Statistical Analysis Used:** Comparison between HIV-1, HIV-2 and HIV-1+2 positive groups for age, gender, route of transmission was made using chi squared test. *P* value < 0.05 was considered as significant. **Results:** Of the total of 66,708 patients tested, 5,238 (7.9%) were positive for HIV antibodies. 7.62%, 0.14%, 0.08% and 0.004% were HIV-1, HIV-2, HIV-1 and HIV-2 co-infected and HIV type indeterminate (HIV-1 Indeterminate, 2+) respectively. The current algorithm could not differentiate between the types of HIV infection (as HIV-1 or HIV-2) in 63 (1.2%) cases. **Conclusion:** In areas like the Indian subcontinent, where epidemic of both HIV-1 and HIV-2 infections are ongoing, it is important to modify the current diagnostic algorithms to diagnose and confirm HIV-2 infections.

Key words: HIV, HIV epidemic, HIV-2, Testing algorithm

INTRODUCTION

HIV-2 was first described in 1985[1] and was isolated in 1986 in West Africa.[2] The HIV-2 epidemic has its epicenter in West Africa, and is also found in those countries that have had historical colonial links with the region, in particular Portugal and France. It has also been reported infrequently in parts of India with previous ties to Portugal.[3]

HIV-2 is associated with lower viral load levels and slower rates of CD4 decline and clinical progression compared with HIV-1;[4,5] 86 to 95% of people infected with HIV-2 are long-term non progressors.[6,7] HIV-2-infected individuals with progressive disease are less likely to respond as predictably to ART as patients with HIV-1 infection.

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The choice of ART for HIV-2 differs from that for HIV-1, underscoring the importance of differentiating between HIV-1 and HIV-2 in patients at risk for HIV-2 infection. Clinical monitoring of HIV-2 is hampered by the absence of assays with Food and Drug Administration (FDA) approval for quantification of HIV-2 viral load, as well as a lack of consensus on interpretation of HIV-2 resistance testing.[8] The current surveillance programs do not report the type of HIV infection. Hence, information about HIV-2 and dual infection in India is limited.

The current study was planned to find out the prevalence of HIV-2 infection at our center over a period of three years, to study the route of transmission in HIV-2 infected patients and to find out the utility of the current diagnostic algorithm in differentiating HIV types.

MATERIALS AND METHODS

Our hospital is a tertiary care referral center and offers a wide range of services for HIV patients such as counseling and testing, free antiretroviral treatment, referral services, monitoring of treatment response with CD4 cell counts,

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follow-up and supportive care of HIV-infected persons. A person desirous of getting tested is offered pre-test counseling and after he/she gives informed consent is tested for presence of HIV antibodies using WHO/NACO HIV testing strategy III.[9] As per this strategy, a person is reported as positive for presence of HIV antibodies only if he is reactive by all three serial tests. The first test identifies the presence of HIV antibodies and the second and third test can identify and differentiate between HIV-1 and HIV-2 types.

A retrospective analysis of data of three years from April 2009 to March 2012 was carried out at our integrated counseling and testing center (ICTC) after obtaining Institutional Ethics Committee approval. All patients diagnosed as HIV infected using NACO/WHO HIV testing strategy III were included in the study for analysis. The patients were classified as HIV-1 infected (HIV-1+ 2 -), HIV-2 infected (HIV-1- 2 +) and HIV-1 and HIV-2 co-infected (HIV-1+ 2 +) based on their second and third test results. For samples which gave discordant results regarding HIV type in the second and third test, immunoblotting result from National Reference Laboratory was considered as final. Comparison between HIV-1, HIV-2 and HIV-1+2 positive groups for age, gender, route of transmission was made using chi squared test. *P* value < 0.05 was considered as significant.

Table 1: Prevalence of HIV infection at integrated counseling and testing center, Mumbai

	2009-2010	2010-2011	2011-2012	Total
Samples tested	18,718	22,805	25,185	66,708
Total positive (%)	1854 (9.9)	1730 (7.6)	1654 (6.6)	5238 (7.9)
HIV 1+/2–(%)	1800 (9.6)	1680 (7.4)	1604 (6.4)	5084 (7.62)
HIV 2+/1–(%)	36 (0.2)	30 (0.13)	30 (0.1)	96 (0.14)
HIV 1+2+(%)	18 (0.1)	17 (0.07)	20 (0.1)	55 (0.08)
HIV 1 *IND 2+(%)	0 (0)	3 (0.01)	0 (0)	3 (0.004)

*IND=Indeterminate

Table 2 Characteristics of individuals with HIV 1, HIV 2 and HIV 1+2 infections

Variable	HIV 1 *n* (%)	HIV 2 *n* (%)	HIV 1+2 *n* (%)	*P* value
Total=*n*5,235	5084 (97.05)	96 (1.83)	55 (1.05)	
Sex				
Males	3294 (64.8)	69 (71.9)	42 (76.4)	0.0748
Females	1788 (35.2)	27 (28.1)	13 (23.6)	
Transgender	2 (0.04)	0 (0)	0 (0)	*
Age(year)				
0-24	529 (10.4)	4 (4.2)	2 (3.6)	0.0002
25-34	1404 (27.6)	19 (19.8)	6 (10.9)	
35-49	2532 (49.8)	52 (54.2)	37 (67.3)	
≥50	619 (12.2)	21 (21.9)	10 (18.2)	
Route of transmission				
Sexual	4799 (94.4)	95 (99)	55 (100)	*
Blood Transfusion	70 (1.4)	0 (0)	0 (0)	
Needle Stick/ Surgery	9 (0.2)	0 (0)	0 (0)	
MTCT	206 (4.1)	1 (1)	0 (0)	

Three samples which were reported as HIV type indeterminate were not included in this analysis, **P* value is not calculated as values in many of the cells are zero

RESULTS

A total of 66,708 patients were tested for the presence of HIV antibodies from April 2009 to March 2012. Of these, 5,238 (7.9%) were positive for HIV antibodies. Of those reported as positive, 7.62%, 0.14%, 0.08% and 0.004% were HIV-1 infected (HIV-1+ 2 -), HIV-2 infected (HIV-1- 2 +), HIV-1 and HIV-2 co-infected (HIV-1+ 2 +) and HIV type indeterminate (HIV-1 Indeterminate, 2+) respectively. There was no change in the prevalence of HIV types over the period of three years [Table 1].

Of the total positive patients, 3,406 (65%) were males and there was no statistically significant difference in HIV types as regards gender. The distribution of HIV types was not uniform across different age groups ($P = 0.0002$). Patients with HIV-2 infection were comparatively older than HIV-1 infected patients. Though the most common route of HIV-2 transmission was heterosexual (95/96), one child (1/96) did have mother to child transmission [Table 2].

The rapid kits used for HIV testing could not differentiate between the types of HIV infection (as HIV-1 or HIV-2) in 63 (1.2%) cases. On immunoblotting, 52 of these were proved to be HIV-1 infected (HIV-1+ 2−), 8 were HIV-1 and HIV-2 co-infected (HIV-1+ 2 +) and 3 were HIV type indeterminate (HIV-1 Indeterminate, 2+).

DISCUSSION

Under the National AIDS Control Program (NACP) of Ministry of Health and Family Welfare, Government of India, single dose nevirapine is given to HIV-infected mother at the time of delivery to prevent mother to child transmission (MTCT) of HIV. Also, the first line of ART given under NACP consists of a combination of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-nucleoside reverse transcriptase inhibitor (NNRTI).[10] HIV-2 is intrinsically resistant to NNRTI such as nevirapine and efavirenz and not all protease inhibitors (PI) provide good viral suppression.[11] The World Health Organization (WHO) 2010 treatment guidelines state that a triple NRTI regimen may be considered in patients with HIV-2 infection.[12] The U.S. Department of Health and Human Services HIV treatment guidelines suggest

starting a boosted-PI regimen[13] but do not specify which drugs should be used. Hence, it is important to know the type of HIV infection before initiating ART in a patient. However, the estimation of HIV types is not usually the main objective of diagnosis or seroprevalence studies, and there are fewer data on HIV-2 than on HIV-1. Therefore, an attempt was made to find out the types of HIV infection using the existing testing algorithm.

Various authors in South and West India have reported that HIV-2 prevalence ranges from 0.3% to 2.1%.[8,14-18] Comparatively, our finding of 0.14% is low. This proves that currently a heterogenous epidemic of HIV-2 exists in India. Also, as there are hardly any studies from North and East India, a large scale multicentric study is required to find out the prevalence of HIV-2 infections in India. This can easily be done by incorporating type discriminatory tests in HIV Sentinel Surveillance (HSS) activity. HSS is conducted every year by NACO across the country to monitor the trends of HIV infection in general population and different high risk groups such as commercial sex workers, intravenous drug abusers, etc.

Studies conducted both in West Africa and India have demonstrated that HIV-2 prevalence is decreasing over a period of years.[18-20] However, the prevalence of HIV-2 and dual infection seen in our study was constant over a period of three years. This may be due to the fact that we have studied the prevalence over three consecutive years whereas other authors have reported it over a gap of 7 to 10 years.

Previous studies have reported mean/median age of HIV-2 positive patients to be higher than that of HIV-1.[8,15,21] Similar findings are observed in the present study [Table 2]. This may be due to the fact that there can be a delay in HIV-2 infected individuals seeking diagnosis and treatment because of the low transmissibility and slower disease progression of HIV-2.

HIV-2 is less infectious than HIV-1, with a five to ten fold lower rate of heterosexual transmission and a 20-30-fold lower rate of vertical transmission. This is likely to be a result of the lower level of viremia observed in HIV-2 than in HIV-1. The most common mode of transmission of HIV-2 is through heterosexual route.[11] Similar findings were seen in our study. We also had one child with perinatal transmission of HIV-2. Hence, in a country like India, which relies solely on nevirapine for its MTCT in its national program, it is imperative to differentiate between HIV types.

The dynamics of interaction between HIV-1 and HIV-2 have been a matter of controversy for decades, and expertise in the area of HIV-1/HIV-2 co-infection remains limited. In geographical regions where a dual epidemic of HIV-1 and HIV-2 is ongoing, the serological reactivity to both the viruses in an infected individual may be a source of diagnostic difficulties.[18] The dual seroreactivity may be due to one of the following reasons, (a) a mixed infection; (b) broad immune response against infection with a single strain of HIV-1 or HIV-2; (c) infection with a unique third virus containing epitopes common to either viruses or (d) exposure to both viruses but established infection with only one.[22] Approximately one percent of positive patients in the current study were reported to be dually infected based solely on serological method. The current diagnostic algorithm does not recommend any further confirmation of dually infected patients. However, Peeters *et al*. have emphasized that the prevalence estimation based entirely on serological methods may overestimate the prevalence of dual infection as indicated in their study which showed that more than half the individuals reactive for HIV-1 and HIV-2 antibodies were only infected with HIV-1 alone.[23] Dual infection can be proven only by the isolation of both viruses from the same individual or by demonstration of HIV-1 and HIV-2 proviral DNA in peripheral blood monocytes by polymerase chain reaction.[11] Grez *et al*. has confirmed the existence of dual infection in India by molecular technique.[24] It was a limitation of our study that we could not confirm the dual infected cases by immunoblotting or molecular technique. Hence, what we need are diagnostic tests which have enough power to discriminate between mono and dual infection and can be performed in an ICTC.

In our study, the current testing algorithms could not differentiate between HIV types in 63 samples and these had to be referred to the National reference laboratory for confirmation by Immunoblotting. Of these, three were HIV type indeterminate. Cross reactivity can occur between HIV-1 and HIV-2 during Western blot analysis because of the 40-60% homology at the nucleic acid and amino acid level leading to indeterminate observation. The dual reactivity in the Western blot may also be due to the recombination of the two viruses.[25] Kannangai *et al*. have reported that the prevalence of HIV-2 is accurately estimated by the use of immunoblotting, but that of HIV-1 and -2 dual infections may be overestimated.[26] However, Qiu *et al*. have reported that HIV-2 Western blot may overestimate the prevalence of HIV-2 in the population with HIV-1.[27] Currently, there is no supplemental HIV-2 antibody test approved by the FDA for *in vitro* diagnostic use in the United States.[3] It was a limitation of our study that we could not follow-up these three HIV type indeterminate patients. Also, in the current algorithm there is no protocol for confirming these type indeterminate samples.

The strength of our study is that it has been conducted in a large number of patients over a period of three years in a programmatic setting which reflects the operational reality of the epidemic.

CONCLUSION

To conclude, it is high time to assess the exact prevalence of HIV-2 infection in our country by incorporating type differentiating assays in the HSS. As perinatal transmission of HIV-2 is also seen, different regimen for the prevention of mother to child transmission is required. Also, the current diagnostic algorithms need to be modified to diagnose and confirm mono and dual infections; otherwise we will have to face serious resistant strains of HIV-2 which will possibly pose a problem in our country in future as the present regimen given in Government ART center amounts to two effective drugs only and not exactly HAART.

REFERENCES

1. Barin F, M'Boup S, Denis F, Kanki P, Allan JS, Lee TH, *et al*. Serological evidence for virus related to simian T-lymphotropic retrovirus III in residents of West Africa. Lancet 1985;2:1387-9.
2. Clavel F, Guetard D, Brun-Vezinet F, Chamaret S, Rey MA, Santos-Ferreira MO, *et al*. Isolation of a new human retrovirus from West African patients with AIDS. Science 1986;233:343-6.
3. Campbell-Yesufu OT, Gandhi RT. Update on human immunodeficiency virus (HIV)-2 infection. Clin Infect Dis 2011;52:780-7.
4. Andersson S, Norrgren H, DaSilva Z, Biague A, Bamba S, Kwok S, *et al*. Plasma viral load in HIV-1 and HIV-2 singly and dually infected individuals in Guinea-Bissau, West Africa: Significantly lower plasma virus set point in HIV-2 infection than in HIV-1 infections. Arch Intern Med 2000;160:3286-93.
5. Marlink R, Kani P, Thior I, Travers K, Eisen G, Siby T, *et al*. Reduced rate of disease development after HIV-2 infection as compared to HIV-1. Science 1994;265:1587-90.
6. De Silva TI, Cotten M, Rowland-Jones SL. HIV-2: The forgotten AIDS virus. Trends Microbiol 2008;16:588-95.
7. Van der Loeff MF, Larke N, Kaye S, Berry N, Ariyoshi K, Alabi A, *et al*. Undetectable plasma viral load predicts normal survival in HIV-2-infected people in a West African village. Retrovirology 2010;7:46.
8. Chiara M, Rony Z, Homa M, Bhanumati V, Ladomirska J, Manzi M, *et al*. Characteristics, immunological response and treatment outcomes of HIV-2 compared with HIV-1 & dual infections (HIV 1/2) in Mumbai. Indian J Med Res 2010;132:683-9.
9. HIV Testing Manual: Laboratory Diagnosis, Bio-Safety and Quality Control NACO. Available from: http://www.nicd.nic.in/writereaddata/linkimages/194.doc. [Last accessed on 2012 Sep 15].
10. Antiretroviral Therapy Guidelines for HIV Infected Adults and Adolescents Including Post Exposure Prophylaxis. National AIDS Control Organisation, Ministry of Health and Family Welfare; Government of India. 2007. Available from: http://www.nacoonline.org/upload/Policies%20&%20Guidelines/1.%20Antiretroviral%20Therapy%20Guidelines%20for%20HIV-Infected%20Adults%20and%20Adolescents%20Including%20Post-exposure.pdf [Last accessed on 2012 Sep 15].
11. Gilleece Y, Chadwick DR, Breuer J, Hawkins D, Smit E, McCrae LX, *et al*. BHIVA Guidelines Subcommittee. British HIV Association guidelines for antiretroviral treatment of HIV-2-positive individuals 2010. HIV Med 2010;11:611-9.
12. World Health Organization. 2010 Guidelines on antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach. Available from: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf. [Last accessed on 2012 Sep 15].
13. Panel on Antiretroviral Guidelines for Adults, and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services; 2009. p. 1-161. Available from: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. [Last accessed 2012 Sep 15].
14. Murugan S, Anburajan R. Prevalence of HIV-2 infection in south Tamil Nadu. Indian J Sex Transm Dis [serial online] 2007;28:113.
15. Agrawal S, Sawant S, Shastri J. Prevalence of HIV-2 infection in Mumbai. Indian J Dermatol Venereol Leprol 2010;76:709-10.
16. Solomon S, Kumarasamy N, Ganesh AK, Amalraj RE. Prevalence and risk factors of HIV-1 and HIV-2 infection in urban and rural areas in Tamil Nadu, India. Int J STD AIDS 1998;9:98-103.
17. Sonth SB, Solabannavar SS, Baragundi MC, Patil CS. The prevalence of HIV–2 seropositivity in blood donors. J Clin Diagn Res [serial online] 2010;4:3091-4. Available from: http://www.jcdr.in/article_fulltext.asp?issn=0973-709x&year=2010&volume=&issue=&page=&issn=0973-709x&id=975 [Last cited on 2010 Oct 31, Last accessed on 2012 Sep 15].
18. Kannangai R, Ramalingam S, Vijayakumar TS, Prabu K, Jesudason MV, Sridharan G. HIV-2 sub-epidemic not gathering speed: Experience from a tertiary care center in South India. J Acquir Immune Defic Syndr 2003;32:573-5.
19. Norrgren H, Cardoso AN, da Silva ZJ, Andersson S, Dias F, Biberfeld G, *et al*. Increased prevalence of HIV-2 infection in hospitalized patients with severe bacterial diseases in Guinea-Bissau. Scand J Infect Dis 1997;29:453-9.
20. Månsson F, Camara C, Biai A, Monteiro M, da Silva ZJ, Dias F, *et al*. High prevalence of HIV-1, HIV-2 and other sexually transmitted infections among women attending two sexual health clinics in Bissau, Guinea-Bissau, West Africa. Int J STD AIDS 2010;21:631-5.
21. Poulsen AG, Aaby P, Jensen H, Dias F. Risk factors for HIV-2 seropositivity among older people in Guinea-Bissau. A search for the early history of HIV-2 infection. Scand J Infect Dis 2000;32:169-75.
22. Kannangai R, David S, Sridharan G. Human immunodeficiency virus type-2-A milder, kinder virus: An update. Indian J Med Microbiol 2012;30:6-15.
23. Peeters M, Gershy-Damet GM, Fransen K, Koffi K, Coulibaly M, Delaporte E, *et al*. Virological and polymerase chain reaction studies of HIV-1/HIV-2 dual infection in Côte d'Ivoire. Lancet 1992;340:339-40.
24. Grez M, Dietrich U, Balfe P, von Briesen H, Maniar JK, Mahambre G, *et al*. Genetic analysis of human immunodeficiency virus type 1 and 2 (HIV-1 and HIV-2) mixed infections in India reveals a recent spread of HIV-1 and HIV-2 from a single ancestor for each of these viruses. J Virol 1994;68:2161-8.
25. Ampofo WK, Koyanagi Y, Brandful J, Ishikawa K, Yamamoto N. Seroreactivity clarification and viral load quantitation in HIV-1 and HIV-2 infections in Ghana. J Med Dent Sci 1999;46:53-62.
26. Kannangai R, Ramalingam S, Prakash KJ, Abraham OC, George R, Castillo RC, *et al*. Molecular confirmation of human immunodeficiency virus (HIV) type 2 in HIV-seropositive subjects in south India. Clin Diagn Lab Immunol 2000;7:987-9.
27. Qiu M, Liu X, Jiang Y, Nkengasong JN, Xing W, Pei L, *et al*. Current HIV-2 diagnostic strategy overestimates HIV-2 prevalence in China. J Med Virol 2009;81:790-7.

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