HIV-2 – AN ENIGMA!

Alaka Deshpande, Mumbai

A new dreadful disease of AIDS was recognized in 1981. It spread globally like a wild fire and assumed pandemic proportion. The causative organism was discovered in 1983-84 and named as Human Immunodeficiency Virus. It is a lymphotropic, cytopathic retrovirus. By 1985, the spectrum of HIV disease became apparent with various minor and fatal OIs.

In 1986 a virus similar to HIV was identified from AIDS patient in West Africa.1 The genomic structure of this virus was different from the HIV discovered in 1984 (Fig. 1).

Hence in 1986, the first virus was identified as HIV-1 and the one discovered later was called as HIV-2. In 1987 Clavel et al showed the association of HIV-2 infection with AIDS.2 Although HIV-1 and HIV-2 are related, there are important structural differences which influence pathogenicity, natural history and the therapy.

EPIDEMIOLOGY

HIV 2 infection is predominantly found in West-African nations, such as Guinea-Bissau. The Gambia, Senegal, Cape Verde, Cote d’ Ivoire, Mali, Sierra Leone and Nigeria. In late 1980s, each of these countries had reported a prevalence of > 1% of the national population.3 Two decades ago it was reported in 8% of adults and upto 20% in individuals above 40 yrs of age.

An estimated 1-2 million people in W. Africa4 are infected with HIV-2. However, recently da Silva et al5 have reported a decline in HIV-2 prevalence in younger people probably due to lower transmission efficiency of HIV-2 compared to HIV-1 as shedding of HIV-2 in genital secretions is significantly lower. Prevalence was highest amongst women in 45-60 yrs age group probably related to hormonal changes in vaginal mucosa.

From W. Africa, HIV-2 may have spread to countries which had historical or socio economic ties with W. African countries.

HIV-2 may have spread from Guniea-Bissau to Portugal during the war of independence. It has been reported from the former Portuguese Colonies such as Angola, Mozambique and Brazil, so also in parts of India which had ties with Portugal such as Goa, Maharashtra. Cases have also been reported from Kakinada. Sporadic cases have been reported from other parts of the country, may be as a result of migration.

[Diagram of genomic structure of HIV-1 and HIV-2]

Fig. 1: Genomic structure of HIV-1 and HIV-2
In United States, the first case of HIV-2 was diagnosed in 1987 in a West African woman who presented with neurotoxoplasmosis. Diagnoses of HIV-2 are increasing in India but the prevalence remains low in US and Europe.

ORIGIN OF HIV-2

HIV-2 closely resembles the Simian Immunodeficiency Virus from the West African sooty mangabey. A simian virus that is thought to have made the transition to humans more than once, yielding eight distinct HIV-2 groups of which only A and B are endemic; the remainder being single person infection. The entry date of HIV-2 subtype A ancestor into human is estimated to be 1940 ± 16 years approximately a decade after the introduction of HIV-1 into human population. Distinct clusters of HIV-2 from infected people living close to sooty mangabey’s natural habitat in Sierra Leone and Liberia closely resemble SIVsm from Monkeys in the same area. Similar clusters have been reported from other countries also.

HIV-2 is an important virus which represents a distinct lineage of HIV, stemming from SIVsm instead of SIVcpz responsible for HIV-1.

RISK FACTORS AND TRANSMISSION

Risk factors and modes of transmission for HIV-2 are the same as those for HIV-1 namely, multipartner unprotected sex, parenteral through infected transfusion, sharing needles in intravenous drug users, and perinatal.

However HIV-2 infectivity is low. A prospective cohort of female sex workers in Senegal, showed a slower rate of heterosexual spread. In Ivory coast, the perinatal transmission of HIV-2 was 1.2% compared to 24.7% in HIV-1.

A recent study in Gambia showed the rate of perinatal transmission of HIV-2 was 4% i.e. 6 fold lower than HIV-1 transmission rate of 24.4% without ARV.

The lower infectivity of HIV-2 is likely related to lower RNA levels of HIV-2.

NATURAL HISTORY

Clavel F et al in 1987 showed that HIV-2 infection was associated with AIDS. Over the years, various studies confirm the fact that the progression to AIDS in HIV-2 infected cases is much slower than HIV-1. It is shown that CD4 decline is much slower in HIV-2 cases than in HIV-1. The rate of progression is highly variable. Two distinct patterns can be identified. A large number of the patients behave more like long term non progressors (LTNP) who remain asymptomatic for 10-20 years without treatment. While a smaller proportion progresses like HIV-1. HIV-2 viral loads on an average are 28 fold lower in recent seroconvertors. However, once advanced immunodeficiency develops, the HIV-2 individuals have a high mortality as seen in study from Gambia.

CLINICAL COURSE OF THE DISEASE

As described earlier, a large proportion of patients remain asymptomatic for a longer duration. They behave like long-term non progressors.

Those who progress more rapidly, experience the same opportunistic infections like tuberculosis, neurotoxoplasmosis, cryptococcosis, esophageal candidiasis, cryptosporidiosis, AIDS dementia complex, PML etc. Interestingly, AIDS defining illnesses have been noted to occur at higher CD4 cell counts.

HIV-1 nephropathy has been reported in 7% of cases while it is a rarity in HIV-2.

DIAGNOSIS OF HIV-2

Serological tests which detect the anti-HIV antibodies are the simplest and less expensive methods for HIV diagnosis. However due to cross reactivity between HIV-1 and HIV-2, the diagnosis of HIV-2 infection by serological tests needs to be done carefully. HIV-2 has a different Capsid antigen from HIV-1 p24 antigen and this antigen may result into prolonged seroconversion window period for HIV-2. But as yet there is no evidence that it may be longer than three months. Certain immunochromatographic tests approved by FDA for HIV-2 diagnosis are used. The dot blot assays should be confirmed with line immune assay or Western Blot.

HIV-2 Western Blot test which is distinct from HIV-1 western blot. However it may give indeterminate results posing diagnostic difficulty. HIV-2 viral load estimation has similar problems. HIV-2 turnover is extremely low with the existence of long-lived latent population. The doubling time is six fold longer than HIV-1 leading to low viral load. Also there is a paucity of commercial viral load assays for HIV-2. Diagnostic algorithm for HIV-2 hence becomes difficult.

MANAGEMENT

HIV-2 is intrinsically resistant to first generation non-nucleoside reverse transcriptase inhibitors. These agents should not be used.

NRTI are active against HIV-2 but due to naturally occurring polymorphisms in reverse transcriptase there may be a variation in efficacy of different agents. HIV-2 seems to have a low genetic barrier to resistance e.g. as few as two mutations in HIV-2 confer full resistance to Zidovudine & Lamivudine. Q151M and K65R may develop much more rapidly in HIV-2 infected cases.

It also has natural polymorphism at many PI codon positions which may play a role in early treatment failure.

In vitro studies have shown IC 50 value for Atazanavir (seven fold) Nelfinavir & Tipranavir (eightfold) to be significantly higher than those for HIV-1. Therefore these compounds have
a lower activity against HIV-2. Amongst the PIs, Lopinavir and Saquinavir have shown to be effective. Reduced susceptibility has been shown to fusion inhibitors. However in vitro phenotypic susceptibility to integrase inhibitors was similar to HIV-1. There is a possibility that HIV-2 may use co receptors other than CCR5 & CXCR4. Therefore efficacy of CCR5 antagonist remains unknown at present.

Therefore as per BHIVA guidelines the treatment suggested for HIV-2 is shown in Table 1.

The treatment should be initiated at a higher CD4 count of 350-500 cells/µl. HIV-2 viral load of 1000 copies/ml is considered high and is the indication to initiate therapy.

OUR EXPERIENCE

As per the national guidelines the Serological reports of HIV infection were given as HIV POSITIVE without differentiating between HIV-1 and HIV-2. Feb 2008, the drugs for second line ARV became available under the national programme. Our experience at the centre of excellence in HIV care at Sir JJ Hospital revealed that 30% of the first line failure cases had immunovirological discordance i.e. low CD4 with low viral load. At this stage the author retested these patients and insisted on having a detail report of HIV testing differentiating between HIV-1 and HIV-2. From Jan 2009 till Sept 2011 we enrolled 129 cases of HIV-2 confirmed by HIV-2 western blot. There are 11 cases of dual infection of HIV-1 + HIV-2. About 54% cases were discordant probably indicating low transmissibility of HIV-2. The patients presented very late with a low CD4 count as a result 16 cases expired within 2 months to less than 1 year of detection. The spectrum of OIs in these cases was similar to HIV-1 with TB being the commonestOI followed by diarrhea, herpes zoster, esophageal candidacies. With limited resources these cases are being treated with 2NRTIs + 1PI. Course of HIV 1+2, a dual infection is similar to HIV-1, however treatment needs to be PI based.

IS HIV-2 AN ATTENUATED VIRUS?

Majority of the patients with HIV-2 infection behave as long-term non-progressors. Is it because of low virulence of the HIV-2? Lower viral load and a good host immune response result into LTNP. However the lymphoid histoculture model did not show any difference in the Cytotoxicity between HIV-1 and HIV-2. Lack of HIV-2 pandemicity is attributed to lower viral load and lower transmissibility. There is some evidence to suggest a better host immune control in HIV-2 infection. Is it related to different co-receptor usage?

Being a pathogenic retrovirus it fails to cause a disease in the majority of infected individuals yet has an ability like HIV-1 to cause AIDS in others. Answers to these questions will result into better understanding of the pathogenesis, of factors enhancing host immune control mechanisms, newer therapeutic targets. Both therapeutic and prophylactic HIV-2 vaccine could act as proof of concept for development of HIV-1 vaccine.

Thus HIV-2 is still a puzzle, an Enigma!

REFERENCES