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HIV-1 Infection and Drug-Abuse in India—An Emerging Challenge

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Abstract: India has a population of over 1 billion and the first cases of HIV-1 infection were reported from there in 1987. Since then HIV-infection has spread there very aggressively and at present it is reported that there may be 5.7 millions individuals infected with HIV. Unlike the western countries where the infected HIV-1 virus belongs to clade B, in India it is clade C. A number of structural and functional differences in these two strains can lead to very different pathogenesis. What we know about pathogenesis due to HIV-1 infection is mostly due to studies carried out in the west where the infecting clade is B. Studies on clade C are very few and to meet this challenge research on HIV-1 C clade infection should be carried out on priority bases. Recently NIH funded projects in India are attempting to initiate research on HIV-1 infection. The epidemiology and belief systems in India are additional challenges to carrying out HIV research. There is an urgent need to initiate multi-disciplinary research.

Key Words: HIV, AIDS, India, Clade C

INTRODUCTION

The HIV-1 pandemic is a major global public health challenge and has affected almost all countries in the world. Recent studies suggest that HIV-1 infection is *now* spreading in the highly populated countries of South East Asia, including India. India, with a population of over 1 billion, reported the first cases of HIV-1 infection in 1987^[1, 2] among commercial sex workers. Over the years, HIV-infection has spread across the general population all over the country and it is estimated that at present there are over 5.7 million infected individuals in India^[3]. Despite an outstanding administrative system in India, some of the cultural traditions, belief systems and multiple medical systems, make it very difficult to manage HIV infection. According to the National AIDS Control Organization (NACO) established by the Government of India in 1992 to carry out India's AIDS Programs, India's HIV epidemic is made up of a number of epidemics since it varies in different states with respect to risk factors. In order to manage HIV/AIDS, the major efforts in India continue to be directed towards primary prevention and therapeutic interventions using antiretroviral therapies (ART). In order to treat individuals with AIDS, NACO has organized regional centers that provide ART

intervention. The number of such centers has steadily increased over the last 3 years and this year the number of such centers is expected to rise to 120. Although the prevalence of HIV-1 infection in India has been estimated to be quite low^[4], various areas of the country continue to report pockets of significantly higher prevalence. India consists of 28 states and 7 federally administered union territories. Each state is divided into administrative units called districts and there are over 602 districts in India. Recent reports from NACO suggest that at present, there is a high prevalence of HIV-1 infection among 163 districts distributed in 20 states located both in southern and northern parts of the country. It has been estimated that annually 20,000 to 30,000 deaths occur in India due to HIV-related causes. The epidemiology of India also is a challenge to enforcing interventions and health awareness in a unified manner. A majority of people in India live in rural areas and speak different languages. There are 18 officially recognized languages and, in addition, multiple dialects are spoken in India. Although due to growth in economy, there has been a significant increase in the population that can be called as middle class, almost 200 million people live in poverty or with very low income. The socio-demographic profile of India suggests that average annual family income is

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equivalent to around \$400 and the average family size consists of 5 individuals, and moreover, about 70% of income is spent on food procurement for the family. The socioeconomic heterogeneity along with a number of languages spoken produces additional challenge in developing a unified approach for intervention and research. In addition, a large proportion of the Indian population is of reproductive age and 35% of the population is below age 15. At the same time gender ratio of males to females is falling and at present it is estimated that for every 1000 males there may be only 915 females. Any rational policy to develop intervention strategy has to take into consideration all of these factors.

Risk-Factors: Multiple risk factors are responsible for the spread of HIV epidemic in India. Data from government sources suggest that over 86% of individuals are infected by unprotected heterosexual sex, 4% with contaminated blood and its products transfusion, and 2% are infected by vertical transmission. Injecting drug use has been reported to lead to HIV infection in about 4% of cases and the cause of infection among 4-6% of patients remains unknown. As far MSM is concerned, this act being illegal in India, until recently information was scarce. However, due to the organization of gay support groups, evidence has started emerging. According to recent stories in the newspapers, MSM may also be present in a significant number, for instance, it has been reported that there are over 2000 MSM in the northern town of Chandigarh. It had long been believed that individuals belonging to certain professions were at high risk of contracting HIV infection. Such professions included cross-country truck drivers and camel drivers. However, at present it appears that HIV-infection has entered the general population of the country. Data collected over the years in Bangalore in South India shows that in a sample of 3000 patients infected with HIV, among infected men only 14% worked as truck or cab drivers. Among women patients over 65% were home-makers and only 10% were commercial sex workers (Satish, K, personal communication).

Drug Abuse: As mentioned above, earlier reports suggested that HIV infection in about 4% cases was caused by injecting drug use (IDU) and IDU was more or less localized in the North Eastern region of the country that included the Manipur, Mizoram and Nagaland areas bordering with China and Myanmar (Burma) where indigenous heroin use is highly prevalent. These areas are near the Golden Triangle and are on the transit route for drug smuggling. Sentinel surveillance carried out by NACO showed an explosive

growth in HIV prevalence among injecting drug users in these areas and has risen to 80% by 1997. These high prevalence rates among IDUs would certainly also increase infection via unprotected sex. Moreover, recent seizures by law enforcement authorities suggest that use of illicit drugs is much more widely spread in India. It is being reported that use of cocaine is steadily increasing among prosperous populations. In central India, smoking poppy-husk may be leading to risky behavior. Opium is being used by a large number of people in northern and western parts of the country. Although exact information remains unknown, the number of migrant workers has also steadily increased in the country and quite a few of them are indulging in injecting prescription pain-killers such as oxycontin. The country has to be proactive in developing intervention strategies for IDUs.

Progression of HIV infection in India: One of the commonalities among HIV infected individuals irrespective of risk factors across all the states in India, seems to be the infecting clade of HIV-1. Depending upon the structure of its *envelope*, HIV-1 can belong to one of the several clades. The clade in the U.S. and most western countries is clade B. In India and many developing countries, clade C is the predominant infecting strain^[5]. In fact, it is estimated that over 50% of all HIV-1 infected individuals globally are infected with clade C. The progression of HIV-1 infection among individuals infected with clade B using plasma viral load and surrogate marker, CD4 cell counts, has been extensively investigated. However, to-date such data on HIV-1 seropositive individuals in India who are infected with clade C are not available and investigations are underway at least in three laboratories including two with which the authors of this report are associated. There are a number of differences in the characteristics of HIV-1 clades B and C that may influence the progression and pathogenesis of HIV-infection. The genetic material of HIV-1 contains 9 different genes and 15 proteins. To productively infect a target cell, HIV must introduce its genetic material into the cytoplasm of the target cell. The process of viral entry into the target cell involves fusion of the viral *envelope* with specific cell surface receptors. The two viral *envelope* proteins gp120 and gp 41, are conformationally associated to form a trimeric functional unit consisting of three molecules of gp120 exposed on the viral surface and associated with three molecules of gp 41 inserted into the viral lipid membrane. Trimeric gp 120 on the surface of the virion binds to CD4 on the surface of the target cell, and this binding results in a conformational change in the envelope protein that, in turn allows binding of virion to a specific subset of chemokine receptors on the cell

surface^[6]. Twelve chemokine receptors can function as HIV coreceptors in cultured cells, but only two are known to play a role *in vivo*^[7]. One of these is CCR5 which is a coreceptor for macrophage-tropic, non-syncytium inducing (R5) viruses. R5 viruses are associated with the mucosal and intravenous transmission of HIV infection. The other coreceptor, CXCR4, binds T-cell-tropic, syncytium-inducing (X4) viruses. X4 viruses are frequently found during later stages of infection with clade B. This is the main mechanism of HIV-1 binding to CD4 cells and the other mechanisms such as via DC-SIGN are involved in spreading HIV-1 infection from the mucosal surface to T cells in lymphatic organs^[8, 9]. Dual-tropic viruses which may use either CCR5 or CXCR4 coreceptors, also exist. R5 viruses are frequently found in early HIV-1 clade B infection, and a switch to X4 strains in the course of disease are associated with rapid CD4 cell depletion^[10]. Individuals deficient in CCR5 receptors can remain uninfected in the face of high-risk exposure to clade B virus^[11, 12, 13]. However, this correlation is not true for other clades including clade C which tends to favor binding to CCR5 even in late stages of disease^[14]. Moreover, it has been suggested that the absence of X4 phenotype among clade C may be a consequence of persistent immune activation by other co-existing infections, which may constantly trigger CCR5 overexpression. Although this concept remains to be proved, it is interesting to note that in India immune activation via earlier infections may also be very common. Thus, the expression and regulation of these coreceptors is of great importance for the understanding of HIV-1 pathogenesis. Moreover, it has been reported that individuals hosting HIV-1 clade C may experience rapid disease progression^[15]. It has also been shown in one study that HIV-1 clade C in India interacts with CCR5 irrespective of HIV disease status and switch from CCR5 to CXCR4 does not take place^[16]. This study investigated 33 HIV-1+ individuals infected with clade C and having CD4 cells in the range of 23 to over 900/ μ l; no difference in the coreceptor usage was observed– it remained CCR5^[16] irrespective of CD4 cell count. Moreover, analysis of V3 sequence of C clade virus from India showed that serine at position 11 essential for binding to CCR5 was present in all the samples and two arginine residues at positions 8, 11 and/or 18 needed for CXCR4 binding were not found in any of the sample tested^[17, 18, 19, 20]. In order to learn the role of coreceptors in relation to clade C infection progression, the authors of this presentation have initiated studies with investigators at Chandigarh. These studies are funded by NIH.

Transactivating protein, Tat, obtained from clades C and B, as mentioned above also differs in its amino acid sequences. Tat can undergo post translational

modifications that include dimerization and polymerization. It can also be oxidized at the cysteine residues, acetylated at the lysine residues and phosphorylated at the serine and threonine residues. Tat obtained from clades C and B differs in contents of these amino acids^[21]. However, it is not known if these differences impart any changes in the functional properties of the two Tat proteins. Recent reports also suggest that antiretroviral drugs including reverse transcriptase inhibitors and protease inhibitors do not inhibit the production of Tat (in clade B infection) which continues to be actively released extracellularly and can be transmitted into the circulation^[22]. As mentioned above, Tat has been shown to play an important role in the neuropathogenesis of clade B infection and to date there are no studies reported on tat obtained from clade C, vis- à -vis neuropsychological deficits.

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