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HIV Infection among Injecting Drug Users (IDUs): Trends in India

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Abstract

The worldwide prevalence of injecting drug users is estimated to be 15.9 million with more than 10 million living in developing and transitional countries. In India, the HIV prevalence among the injecting drug users has been reported to be as high as 68% in certain cities and among the high-risk groups, IDUs still have among this highest prevalence of HIV. This review outlines the HIV prevalence, primary drug resistance, drug trafficking routes and their implications among the injecting drug users in India.

Key words: Injecting drug users; HIV and IDUs; Drug trafficking routes; Primary drug resistance.

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Introduction

The number of injection drug users (IDUs) worldwide was estimated as approximately 15.9 million (1), of which, over 10 million live in developing and transitional countries. China, USA and Russia have an estimated 2.4 (range: 1.8 – 2.9) million, 1.9 (range: 1.3 – 2.6) million and 1.8 million (range not available) IDUs, respectively, and are believed to harbor the largest population of IDUs in the world (2). In India, it is reported that the absolute number of IDUs is as high as 1.1 million (3). Injection drug use in India was initially recognized in the Northeastern (NE) States of Manipur and Nagaland, likely due to their proximity to the 'Golden Triangle' – Burma, Thailand and Cambodia (4). However, reports document a high prevalence of HIV among IDUs in Tamil Nadu (5, 6) and Maharashtra (7) and recent report suggests the emerging epidemics in the Northern States of Punjab and Haryana (8) which borders Pakistan and Afghanistan.

The most common drug injected worldwide is heroin (diacetylmorphine) (2); also other drugs (e.g., cocaine, methamphetamine, pharmaceutical drugs) are injected with striking regional differences in the type of drug injected. In India, heroin and other pharmaceutical agents (e.g., buprenorphine, dextropropoxyphene, etc.) (6, 9) are commonly used. Pure heroin is very expensive and thus "Brown sugar", an adulterated form of heroin, is the most commonly injectable form of heroin in India. Recently in the NE regions (9) the use of Spasmoproxyvon® (dextropropoxyphene) has been increasing, and Tidigesic® (buprenorphine) is also a common drug of abuse as it is freely available over the counter (OTC) (5). The OTC availability of many drugs in India has resulted in IDUs shifting from one drug of abuse to another when there is a shortage of one agent (10). Also among the Indian injectors majority of them are males; however, reports of injecting drug abuse among women in Delhi and the NE States also exist (11).

HIV prevalence among IDUs

More than 20% of HIV prevalence has been reported among IDUs in 25 countries and territories (12). In fact, the fastest growing HIV epidemics in the world today – namely the epidemics in the former Soviet Union countries – can be attributed to injection drug use (13) and worldwide 9 countries (Argentina, Brazil, Burma, Estonia, Indonesia, Kenya, Nepal, Thailand and Ukraine) are believed to have HIV prevalence greater than 40% among IDUs (2). The spread

of HIV infection among and from IDUs has become an alarming threat in Asia (14). The IDUs and HIV prevalence among the South-East Asian countries are given in the Table 1. A report suggests that the prevalence of HIV among IDUs has increased substantially in Thailand, Myanmar, China, Malaysia, Vietnam and India, since it was first detected in 1988 (14). As per the recent estimate, there are ~2.3 million persons living with HIV in India (15), and heterosexual transmission accounts for 84% of infections and it has gradually disseminated over the years from sex workers to monogamous housewives; however, among the high-

Table 1 : HIV infection among General and IDUs in the Southeast Asian Countries

	IDU Population %[#]	HIV Prevalence in General Population %	HIV Prevalence % among IDU Population	HIV Prevalence % among spouses of IDUs
Afganistan	0.24	0.01	nk*	nk
Bangladesh	0.13	0.1	0.2 - 2.5	nk
Brunei D	1.42	0.1	3.8	nk
Cambodia	0.01	0.6	nk	nk
India	0.21	0.28	1.3 - 68.4	5[@] - 45%[$]
Indonesia	0.42	2.4	15.0 - 47.0	nk
Iran	0.51	0.1	0.5 - 0.7	nk
Laos	0.28	0.1	0	nk
Malaysia	1.47	0.4	10.0 - 40.0	nk
Myanmar	0.71	1.02	37.1 - 63.0	nk
Nepal	0.30	0.5	45.0 - 60.0	nk
Pakistan	0.59	0.1	0.0	nk
Philippines	0.04	0.1	1.0	nk
Singapore	0.48	0.2	1.7	nk
Sri Lanka	0.22	0.1	nk	nk
Thailand	0.11	0.05	20.0 - 56.0	nk
Timor	0.02	0.1	nk	nk
Vietnam	0.23	0.5	0.0 - 89.4	nk

[#] Aceijas *et al.* 2004 (12)

[@] Panda *et al.* 2007 (41)

[$] Panda *et al.* 2000 (23)

* Not Known

Table 2 : Rate of Amino acid substitutions at the Drug Resistance Positions in ART naïve General HIV population and in IDUs

Codons	Rate of amino acid substitutions at drug resistance positions in IDUs (%)	Rate of amino acid substitutions at drug resistance positions in general HIV Population (%)	Reference	p-value*
NRTI				
M41	1.8	2.5	Lall *et al.* 2008 (49)	0.667
		1.0	Shafer *et al.* 2007 (32)	0.532
K65	1.8	0.1	Shafer *et al.* 2007	0.11
D67	0	2.5	Lall *et al.* 2008	0.421
T69	1.8	0.04	Shafer *et al.* 2007	0.047
M184	1.8	2.5	Lall *et al.* 2008	0.667
		0.2	Shafer *et al.* 2007	0.161
L210	3.6	2.0	Balakrishnan *et al.* 2005 (24)	1
T215	0	2.8	Rajesh *et al.* 2009	0.552
		0.3	Shafer *et al.* 2007	1
K219	0	0.1	Shafer *et al.* 2007	1
NNRTI				
A98	1.8	2.5	Lall *et al.* 2008	0.667
K101	1.8	0.3	Shafer *et al.* 2007	0.176
K103	0	0.3	Shafer *et al.* 2007	1
V106	0	0.2	Shafer *et al.* 2007	1
G190	0	0.1	Shafer *et al.* 2007	1
		2.8	Rajesh *et al.* 2009	0.552
PR				
G73	1.8	0.02	Shafer *et al.* 2007	0.029
V82	0	2.5	Lall *et al.* 2008	0.421
L90	0	0.1	Shafer *et al.* 2007	1

* Significant difference in amino acid substitutions between General HIV population and IDUs.

Table 3 : Rate of Amino acid substitutions at the polymorphic Positions in ART naïve General HIV population and in IDUs

	Rate of Polymorphism in IDUs % (Iqbal *et al.* 2009)	Rate of Polymorphism in General HIV population % (Kantor *et al.* 2005)	p-value*
RT Region			
V60	98.2	37.2	<0.0001
S48	94.5	89.8	0.25
K122	90.9	Not Specified	<0.0001
T200	85.5	93.4	<0.02
D177	80	83.9	0.44
K173	80	91.9	<0.02
D121	67.3	19.8	<0.0001
Q207	69.1	91.8	<0.0001
K49	56.4	Not Specified	<0.0001
T39	56.4	98.6	<0.0001
V35	54.5	99.8	<0.0001
E36	49.1	76.9	<0.0001
D123	12.7	61.9	<0.0001
K166	32.7	21.8	0.06
Q174	12.7	30.2	0.005
E194	3.6	2.9	0.74
R211	12.7	66.2	<0.0001
PR Region			
I93	89.2	95.4	0.08
L89	91.8	85.5	0.2762
H69	100	99.4	0.1174
L63	100	Not Specified	<0.0001
Q61	5.4	8.5	0.5087
R41	89.2	93.2	0.3391
M36	97.3	91.4	0.2018
L19	73	Not Specified	<0.0001
G16	5.4	7.9	0.5821
I15	73	83.3	0.0984
K14	70.3	16.7	<0.0001
I13	8.1	Not Specified	<0.0001
T12	81.1	70.1	0.1507

* Significant difference in amino acid substitutions between General HIV population and IDUs.

risk groups, the HIV prevalence has always been the highest among IDUs (more than 10%), as per National AIDS Control Organization (NACO), India (16). In India, IDUs have always taken the backseat in the planning of treatment and prevention programmes. It is only in the North East regions of India, where the epidemic is driven by drug-use, that IDUs receive appreciable attention (17). The estimates of HIV prevalence among Indian IDUs encompass a broad range from 1 to 68% (3), with recent national estimates suggesting 15% HIV prevalence among IDUs greater than 25 years of age (18, 19). Observational studies have reported HIV prevalence among IDUs as high as 80% in some groups (20, 21, 22) in India; however, very sparse data are available on HIV prevalence among IDUs in central India. A study from Kolkata showed a high (45%) transmission of HIV from IDUs to their sexual partners, where the HIV prevalence among IDUs was 80% (23). It is possible that there are concentrated HIV epidemics among IDUs in many regions of India that have not yet been identified. Tamil Nadu accounts for 8% of the HIV disease burden in India (15). Even though the heterosexual route was reported with majority of HIV infections in Tamil Nadu, cases of HIV among IDUs have been reported since the 1990s. Based on the NACO sentinel surveillance data, the prevalence of HIV among IDUs in Tamil Nadu has fluctuated between 18% and 64% between the years 2003 and 2007 (15). A more accurate assessment of HIV prevalence among IDUs was obtained through population-based studies. In the year 2000 HIV prevalence among Chennai IDUs was estimated to be 21% (5) and it was characterized that heroin injectors were more likely to test HIV positive compared with buprenorphine injectors (26% vs 12 %; p=0.09). In 2003, Panda and his colleagues have reported 30% HIV prevalence among 226 married IDUs, with estimating the prevalence of HIV among their spouses to be 5%; also higher HIV prevalence was found to be significantly associated with having injecting drugs at dealers place. In both of these studies, high levels of risk behaviors were described including needle sharing and unprotected sexual intercourse (5, 21).

Primary drug resistance among IDUs

The increased availability of antiretroviral drugs to treat HIV/AIDS in developing countries is expected to contribute to a global rise in drug-resistant HIV strains. Understanding the existence of HIV-1 drug resistance is essential to develop new antiretroviral drugs and optimize the use of existing

drugs. In India, highly active antiretroviral therapy (HAART) has dramatically improved survival and quality of life in HIV infected individuals (24). However, these benefits can be greatly compromised by the drug-resistant forms of the virus. Primary HIV-1 drug resistance was prevalent among IDUs in developed nations; the reports from New Haven (25), Quebec (26), Baltimore (27) and Rio de Janeiro (28) have shown 31%, 24%, 6% and 7.9% primary drug resistance respectively. A recent report from China (29) had shown several polymorphisms, but no drug resistance associated mutations were observed among those IDU population. From the Chennai IDUs primary drug resistance mutations were reported (30) conferring resistance to commonly used Nucleoside Reverse Transcriptase inhibitors (NRTI) such as Zidovidine (ZDV), Stavudine (d4T), didanosine (ddi), Abacavir (ABC), Lamivudine (3TC), Emtricitabine (FTC) and Tenofovir (TDF). In the protease (PR) region mutation were observed conferring resistance to Saquinavir (SQV), Atazanavir (ATV) and Nelfinavir (NFV). The detailed list of amino acid substitutions at the drug resistance positions are compared with substitutions observed among HIV patients (general population), who were ARV naive are given in the Table 2. Significant differences were observed at positions T69 and G73 in the RT and PR regions respectively. Widespread use of antiretroviral drugs can impose selective pressure on *pol* gene, which can lead to subtype specific mutation selections. These inter-subtype polymorphisms will have impact on drug susceptibility and fitness of HIV-1 variants. These forms can be transmitted which can pose a challenge to the successful management of HIV disease. A list of polymorphism observed among the IDUs is compared with the polymorphisms observed in general populations are given in the Table 3. Further, the study has shown that the polymorphisms observed with Chennai IDUs are significantly ($p<0.0001$) different from universally established subtype C-specific polymorphisms (31) at positions V60, K122, D121, Q207, K49, T39, V35, E36, D123, R211 and at positions L63, L19, K14, I13 in RT and PR regions respectively. Also, the substitutions K122E/EK (90.9%) and K49R/KR (56.4) in RT region and L63A/S/T/P/PS/ST/LP (100%), L19I/V/IM/T (73%) and I13V/IV (8.1) in PR region were observed in this study that was not specified in established polymorphisms. These observations reveal that HIV-1 polymorphisms differ in different geographic locations and different population groups within the same subtype. This could be due to the region specific differences as these polymorphisms are associated with host

immune response, geographic and environmental factors (31, 32), mainly in the absence of antiretroviral (ARV) drug. Phenotypic studies are needed to better define these genetic variations and their potential impact on drug susceptibility and clinical outcomes in treated individuals.

Drug trafficking routes

The Indian geographical position is unique in relation to drug trafficking routes as it is geographically situated between two largest heroin producing regions 1) the golden crescent comprising Afghanistan, Iran and Pakistan; and 2) the Golden Triangle comprising Burma, Thailand, Vietnam and Laos (33). Although the "Golden triangle" accounted for larger production of heroin from the early 1950s, today Afghanistan is one of the largest suppliers of heroin in the world. Heroin from Afghanistan has been reported to enter India through Pakistan. According to the 2008 World Drug Report, Afghanistan produced 8,200 metric tons of opium in 2007—the largest in the world—and a large proportion of this trafficked via Pakistan to India. This report also suggested that Asia was the largest market for consumption of heroin, with India being the largest consumer in the region (~3 million opiate users) (34). It is believed that the Taliban who were initially against the production of poppy are now in favour of poppy cultivation as they see it as a valuable source of generating income. Therefore, it is clear that drug-trafficking routes for heroin exist in India, which is distinct from the routes used for trafficking drugs from the "Golden Triangle". It can be hypothesized that heroin from Afghanistan enters India through cities such as Mumbai and Delhi and is then shipped down to the South. Trucks are usually among the preferred modes of transport for trafficking drugs through a country along highways. The Southern most State in India is Tamil Nadu. Due to its proximity to Sri Lanka, it plays a key role in drug trafficking to Sri Lanka from where drug are shipped to Africa. There have also been reports in the local media of the presence of club drugs – ecstasy, amphetamines, and cocaine in India. However, the use of these drugs has been restricted almost exclusively to the higher strata of the society – a group where there is almost no information available on HIV or its associated risks. This hypothesis is also evidenced by HIV-1 subtypes among the IDUs in India, there are reports (35-37) on Thai-B, B/C recombinants from the north east, the similar subtypes have been reported from Burma, Thailand, and Laos in these regions, HIV is believed to have invaded from the IDUs population from the golden triangle along the drug trafficking

routes (38) but in rest of India the predominant subtype was reported to be of subtype C with the recent report of C subtype from Chennai IDUs (39).

Implications of rising HIV prevalence among IDUs

India is at a crucial stage in the fight against the HIV epidemic. It appears that India has performed extraordinarily in controlling the heterosexual epidemic – the epidemic that is most visible. It is time to focus on epidemics among IDUs in various parts of the country that are commonly overlooked. It is encouraging that IDUs are a focus of the current National AIDS Control Programme (NACP-III) (19); however, efforts need to be made to ensure that the plan becomes a reality. The USA is facing a similar situation today. In the early days of the epidemic, men who have sex with men and IDUs contributed maximum to the HIV epidemic. Consequently, most prevention measures were focused on these populations. Today, minority heterosexual women, a population that was seldom given any importance in the early days of the HIV epidemic, have one of fastest growing epidemics in the USA. Epidemics among IDUs have the ability to spread rapidly into the general population – from IDUs to their spouses and sexual partners, as has been observed in the NE regions in the past (23). The majority of IDUs were economically disadvantaged, and are often separated from their families during the period of drug use. This condition of mobile nature makes them particularly vulnerable to infections (e.g., hepatitis A and other diarrhoeal diseases) with limited access to care and drug user treatment (20, 40) In addition, the spouses/sexual partners of these IDUs are in danger of HIV transmission as majority of Indian injectors are males and condom use with regular sexual partners are relatively rare. These group of women are susceptible to HIV, HBV and HCV through their sexual partners risk behaviors, with out their own injecting drug practices. A recent study (41) from Chennai has observed 1% syphilis among IDUs and 2% among their spouses; 40% and 38% of IDUs and their spouses are infected with HSV-2. Hence it is imperative that interventions should also target IDU's spouses / families who are clearly at risk of contracting infections diseases.

Controlling HIV incidence and risk behaviors among IDUs can be achieved in two ways 1) setup and implementing Voluntary Counseling and Testing (VCT) centres in areas where IDUs are prevalent, like the cohort in North Chennai, which is endemic for all the infectious diseases due to crowded conditions and poor sanitations. The

VCT centres for HIV have been shown to be associated with reductions in risk behaviors across many settings in Chennai among high risk population (42, 43). Also there should be established links between these VCT centres with local NGOs that provide substitutions therapy and detoxification for IDUs. Another way of intervention can be made through 2) educating pharmacist to refer IDUs to VCT centres where the IDUs visit for procuring syringes and needles. These pharmacists must be trained in risk reduction counseling and management of heroin overdose, also flyers/posters on safe injection practice can be made available to IDUs through pharmacies. These practices would help much in declining risk behaviors among IDUs. Also the ARV experienced IDUs harboring drug resistance strains may represent the primary source of transmitted HIV drug resistance to their spouses and to uninfected IDUs. The HIV-1 polymorphisms may differ in different geographical locations and population groups within the same subtype. The polymorphisms among IDUs could be region-specific, as the existence of these polymorphisms could be associated with host immune response, as well as geographical and environmental factors (32, 44). Also these polymorphisms are associated with disease progression and response to antiretroviral therapy (44).

Treatment challenges with IDUs

Co-infections with HCV and HBV are huge concern in the clinical management of HIV infected IDUs. Among the Chennai IDUs the prevalence of HBV and HCV was 34% (5) and 62.1% (4) respectively. Although improvements in ARV have led to decreased HIV-related mortality, liver-related morbidity and mortality have increased among co-infected patients (4). The following are the major cofactors that could complicate the management of HIV: 1) The high prevalence of TB is associated with increased risk of mortality especially among IDUs (45) and also TB drugs are hepatotoxic (46). 2) The commonly used HAART in India is fixed dose combination of d4T, 3TC and Nevirapine (NVP) due to its low cost, which is also associated with hepatotoxicity, which may give rise to further complications in HIV/HCV coinfected patients. 3) Malnutrition is common among Chennai IDUs, which can increase the risk of mortality. 4) The high prevalence of alcohol consumption and active injection drug use could impact for non adherence (47, 48).

5) Primary drug resistance could also pose major challenge for successful therapy, screening drug resistance before beginning ARV could be beneficial.

Future prospective:

The areas with high Injecting drug use are among the fastest growing HIV epidemics in the world. The evidence of increased production of injecting drugs and growing drug trafficking routes are threatening as there could be the emergence of new HIV epidemic in these regions. The available data suggests that injection drug use is a major public health problem in India especially in region outside the north east, which is coupled with a high prevalence of HIV and blood borne infections. Longitudinal studies in India are highly needed 1) to estimate HIV incidence, 2) to study natural history of HIV among IDUs, 3) to study other blood borne infections, 4) to examine patterns of substance abuse overtime and 5) will be helpful to estimate morbidity and mortality among HIV positive and negative IDUs. This information will help in developing treatment interventions for IDUs in India.

Interventions must be tuned up to improve access to VCT centres for IDUs in Indian settings. Effective measures must be taken to reduce and manage heroin overdose. It will be also essential to measure and characterize liver disease burden (e.g., liver function tests, liver disease staging and HCV RNA quantification) among Indian IDUs as in India there are different circulating subtypes of HIV (Subtype C) and HCV (Genotype 3) when compared to western world, and in addition the unique local condition such high rate of co-morbidities and alcohol consumption may play a crucial role in the incidence of liver disease in this population. To conclude, it is essential that active steps must be taken to identify these hidden epidemics and provide them with appropriate treatment and prevention.

Authors Contributions:

Prof. Suniti Solomon and Dr. Sunil Suhas Solomon have compiled and reviewed the manuscript. Dr. Balakrishnan Pachamuthu and Dr. Syed Iqbal Hussain have collected the literature and reviewed the manuscript.

Conflict of Interest:

Nil

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