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### Seroprevalence of HIV Infection among Leprosy Patients in Agra, India: Trends and Perspective<sup>1</sup>

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#### ABSTRACT

This study compares the results of HIV seroprevalence, which was carried out in two phases, i.e., 1989 to 1993 and 1999 to 2004. Although the number of leprosy patients screened for HIV infection in the second phase is less (2125) as compared to those screened during the first phase (4025), a rise in HIV infection from 0.12% to 0.37% is certainly disturbing since this area appears to be endemic for both the infections. During the study period, the Out Patient department attendance of a few types of leprosy patients like borderline and borderline lepromatous have risen, whereas others like borderline tuberculoid and polar tuberculoid have declined in the second phase as compared to that of the first phase. The trend over a decade suggests that HIV infection is low among the leprosy patients when compared with other risk groups. Follow-up of these patients at an interval of six months, revealed that none of them downgraded into a severe form of leprosy nor developed ARC or AIDS. In this study, it appears that neither infection precipitated the other. The occurrence of downgradation as well as reversal reactions and neuritis (both chronic and acute) was not observed among the leprosy patients. None of them developed erythema nodosum leprosum reactions. Similarly, the HIV-positive leprosy cases did not develop either AIDS related complex (ARC) or full blown case of AIDS.

#### RESUME

Cette étude compare les résultats de séroprévalence du VIH, obtenus en 2 phases distinctes : de 1989 à 1993 et de 1999 à 2004. Bien que le nombre de patients testés pour l'infection par le VIH soit moindre dans la seconde phase (2125) que dans la première (4025), une augmentation de prévalence de 0.12% à 0.37% est préoccupante puisque la région étudiée est endémique pour les 2 infections. Pendant la durée de cette étude, si la seconde phase est comparée à la première, la présentation de patients au service de Consultations Externes a augmenté pour quelques types de patients lépreux comme les patients borderline et borderline lépromateux et diminué pour les patients borderline tuberculoïdes et tubercu-

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loïdes polaires. La tendance dégagée sur une décennie suggère que l'infection par le VIH est faible chez les patients lépreux, comparés à d'autres groupes à risque. Le suivi tous les 6 mois de ces patients indique qu'aucun d'entre eux n'a rétrogradé en une forme sévère de la lèpre ou n'a développé le complexe associé au SIDA (ARC) ou le SIDA. Dans cette étude, il apparaît qu'aucune de ces infections ne précipite l'autre. Il ne fut pas observé de déplacement vers le bas le long du spectre immuno-pathologique ou de réactions inverses ou de névrites (à la fois chroniques ou aiguës) parmi les patients hanséniens. Aucun n'a développé de réaction de type érythème noueux lépreux. Concomitamment, les cas de lèpre aussi positifs au VIH n'ont développé ni de syndrome ARC ni de SIDA terminal.

### RESUMEN

Este estudio compara los resultados de una encuesta sobre la prevalencia del VIH en pacientes con lepra, realizada en dos fases, la primera de 1989 a 1993 y la segunda de 1999 a 2004. Aunque el número de pacientes investigados para VIH fue mayor en la primera fase (4025) que en la segunda (2125), se notó un incremento en la infección por VIH de 0.12% a 0.37%. Esto es preocupante porque sugiere que esta área es endémica para las dos enfermedades. En la segunda fase del estudio, se observó un incremento en el número de pacientes BL/LL que acudieron al Instituto y una disminución en el número de los pacientes BT/TT. Los resultados globales indican que la infección por VIH es baja entre los pacientes con lepra en comparación con la infección en otros grupos de riesgo. El examen de estos pacientes a los 6 meses de seguimiento reveló que ninguno de ellos "se degradó" a una forma más severa de la lepra, ni desarrolló los signos del complejo asociado al SIDA, ni la enfermedad en sí. Además, ninguna de las enfermedades precipitó a la otra. Ninguno de los pacientes desarrolló reacciones reversas (neuritis agudas y crónicas), ni eritema nodos leproso (ENL).

India has the largest number of known cases of leprosy and happens to incidentally be endemic for HIV as well. Some of the earlier studies done in North and North-Eastern India did not find any association of HIV infection with leprosy patients (24). A few studies from South Indian states showed a higher prevalence of HIV infection among leprosy patients, but these studies alone do not provide any indication of its association with leprosy (12). Leprosy caused by *Mycobacterium leprae* has an unusually long incubation period, and infection with HIV leads to a profound drop in CD4+ T-lymphocyte count and function and compromises the cell-mediated immune response, as well (19,25). Earlier studies carried out in this center suggested that 1 per thousand (5/4025: 0.124%) of the leprosy patients harbored HIV infection. Follow-up of these patients at an interval of six months, revealed that none of them downgraded into a severe form of leprosy nor developed ARC or AIDS (10). Although this study indicated that leprosy is not a risk factor for developing HIV-1 infection, the HIV surveillance studies on this population was continued with a view to assess the risk and find out the trend in an area where both

the infections are prevalent. This study compares the results of HIV seroprevalence, which was carried out in two phases; first, from April, 1989 to March, 1993 when HIV infection was being detected in India in different risk group populations to assess the risk among leprosy patients, and then from September, 1999 to March, 2004. This is the first report of a decade of HIV screening of leprosy patients in this region of the country and the longest follow-up of HIV-leprosy co-infected cases.

One of the commonly observed complaints among leprosy patients was pain in the joints. Many studies have proven that microbial agents might trigger the autoimmune phenomenon and induce rheumatoid arthritis (1,5,8). In order to find out if arthritis is present in the HIV-leprosy co-infected patients, the sera from these cases were tested for Rheumatoid arthritis (RA) factor. Many risk behaviors as well as the routes of transmission for HIV, Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infection are identical to those for other sexually transmitted diseases (STDs) (3). For this reason, the leprosy sera samples were tested for HBsAg and VDRL simultaneously with HIV.

## MATERIALS AND METHODS

Leprosy patients, across the spectrum, i.e., tuberculoid (TT), borderline-tuberculoid (BT), mid-borderline (BB), borderline-lepromatous (BL), lepromatous (LL) and neuritic (N) types, classified, according to Ridley-Jopling criteria<sup>(23)</sup>, attending the Unit-I of the Outpatient's Department (OPD) of the Central JALMA Institute for Leprosy and other Mycobacterial Diseases (CJILOMD) were included in the study. The leprosy cases in the study were neither newly admitted nor untreated patients, although a few were newly detected cases. For bacteriological determination, the six skin sites used were the two ear lobes and four representative active skin sites, i.e., hand (right arm and left arm), elbow (right and left), back, forehead, and the site of the lesion. In our OPD, four skin sites are routinely used for determination of the bacteriological index (B.I.). The inclusion criteria were: adult leprosy patients between the age group of 16 to 48 yrs. Children and old patients were excluded from the study as it was assumed they were not likely to be sexually active. In order to ensure that the patients were not screened over and over again, their OPD cards were marked, "HIV-Screened." This helped in excluding the repeat testing of the patients. Blood was collected aseptically from leprosy patients by ante-cubital venipuncture after obtaining pre-informed consent. The sera samples collected after centrifugation at 2500 g were stored at -20°C until the assays were performed. ELISA was done using Genedia HIV-1/2 EIA kit (Greencross, Korea). Those found positive were confirmed by rapid (HIV capillus latex aggregation assay, Trinity Biotech PLC, Ireland) and Western blot assays (WesternBlot, BIO-RAD, NEWLAVBLOT), Nippon Bio-Rad Laboratories, Japan. After post-test counselling, a report was handed over to those found HIV-positive and patient was referred to clinicians for further care and management. To find out any other co-infections, the samples were further tested by HBsAg kit, (Immuno-chromatography test ERBA Hep-line, Transasia Bio-Medicals Ltd., Mumbai, India) and VDRL and Rheumatoid Arthritis kits (Carbogen and Rhelax, RF of Tulip Diagnostics (P) Ltd., Bambolim, Goa, India).

## RESULTS

The prevalence of HIV-1 infection in leprosy patients was observed in two phases. In phase one, 4025 patients [30 indeterminate (I), 141 polar tuberculoid (TT), 1888 borderline tuberculoid (BT), 409 borderline (BB), 600 borderline lepromatous (BL), 751 polar lepromatous (LL), 200 N] were screened between 1989 and 1993, out of which only 8 were ELISA positive and 5 were Western Blot reactive. Subsequently, in the second phase from 1999 to 2004, 2125 patients (21 I, 19 TT, 646 BT, 332 BB, 610 BL, 324 LL, 173 N) were screened, out of which 8 were ELISA positive and 5 were Western Blot reactive (Table 1). The variation in the results of the two tests correlated well with the titre of HIV-1/2 antibodies in the sera samples. The strongly positive samples having a high absorbance value, ranging between 1.5 and 2.0, measured in terms of O.D. at 450 nm in an ELISA reader had an excellent pattern of reactivity in Western Blot. The samples with weak or moderate positivity in ELISA, with an O.D. ranging between 0.5 and 0.7, did not react with Western Blot. A rise in HIV infection from 0.124% to 0.376% was observed. Two samples were reactive to HIV-2 by Western Blot. Among all the HIV-positive leprosy patients, there were no other co-infections like Hepatitis B, Syphilis and RA. Out of the 8 HIV-leprosy co-infected patients, 2 each were BT and BL types, 3 were BB and 1 was LL type of leprosy.

The predominant clinical features were hypo-pigmented lesions, clawing of fingers and toes, pain, and hand muscle atrophy. Whereas 4 patients had deformity in hands, only one of them reported acute pain. All the patients completed a full course of standard anti-leprosy multi-drug therapy, responded satisfactorily, and were later clinically and bacteriologically negative. The initial bacterial index, prior to treatment, which ranged between 2+ and 3+ became negative on completion of the treatment. Two of the 8 HIV-leprosy co-infected patients (BL, LL) became bacteriologically negative after 6 months and another 2 (BT, BL) became negative after 24 months of treatment (Table 2). We have observed that following treatment, B.I. became negative even in BL and LL cases. The HIV-positive

TABLE 1. *The phase-wise screening of leprosy patients for HIV-1/2 infection.*

I Phase <sup>a</sup> (N = 4025)	HIV status		II Phase <sup>b</sup> (N = 2125)	HIV status	
	EIA	WB		EIA	WB
Borderline-			Borderline-		
Tuberculoid (BT) 1888 (46.90%)	2	2	Tuberculoid (BT) 646 (30.48%)	2	1
Tuberculoid (TT) 141 (3.50%)	1	1	Tuberculoid (TT) 19 (0.89%)	0	0
Indeterminate (I) 30 (0.74%)	0	0	Indeterminate (I) 21 (0.98%)	0	0
Lepromatous-			Lepromatous-		
Leprosy (LL) 751(18.65%)	1	0	Leprosy (LL) 324 (15.24%)	2	2
Borderline-			Borderline-		
Lepromatous(BL) 600 (14.90%)	1	0	Lepromatous (BL) 610 (28.70%)	2	1
Mid-			Mid-		
Borderline (BB) 415 (10.31%)	0	0	Borderline(BB) 332 (15.62%)	2	2
Neuritic (N) 200 (4.96%)	0	0	Neuritic (N) 173 (8.14%)	0	0

<sup>a</sup>denotes I Phase of HIV screening of the leprosy patients which was from April, 1989 to March, 1993.

<sup>b</sup>denotes II Phase of HIV screening of the leprosy patients which was from September,1999 to March, 2004.  
EIA = ELISA, WB = Western Blot.

patients are being followed up at six month intervals. On follow-up, to date none of the patients with HIV-1 infection have progressed into a more severe form of the disease. None of the co-infected cases have been lost so far in follow-up. In these co-infected patients, it is difficult to assess which infection occurred first. Our results indicated that HIV-1 infection does not contribute in any way to the precipitation of serious forms of leprosy.

### DISCUSSION

It is well recognized that HIV infection constitutes a major risk factor for tuberculosis (TB) and for other mycobacteria, such as *M. avium* and *M. intracellulare*, but there are still uncertainties regarding its association with leprosy. The association between the HIV and tuberculosis and certain other non-tuberculous mycobacterial infections have been established (20, 21). Potential effects of HIV infection on leprosy have been suggested and discussed by several authors but, despite expectations, little interaction has been observed upto now (9, 17, 22). Although an association between HIV and leprosy has been described in Zambia (18) and in Tanzania (27, 28), there is some evidence from studies in Mali (15), Ethiopia (6, 7) and in other African countries that HIV infection is not a risk factor for leprosy (14, 16). On the contrary, a few studies carried out in some African countries to determine the as-

sociation between leprosy and HIV infection suggest that HIV infection is an important risk factor for leprosy (4, 18). Some of these studies had limitations in study design and some found no association between the two diseases (2, 13).

The increase in HIV infection as compared to that of the first phase is disturbing and the mode of transmission appeared to be heterosexual as revealed during the post-test counselling session. None of the co-infected cases admitted to having a homosexual relationship or had a history of blood transfusion. Two of the males had symptoms of STDs at the time of testing.

The trend over a decade suggests that HIV infection is low among the leprosy patients when compared with other risk groups, like TB patients, which is 4.3% (26/600) in Agra (in press). The prevalence and incidence for HIV infection in Agra varies in different groups. Our institute has a Voluntary Confidential, Counselling and Testing Center (VCCTC), a State body of the National AIDS Control Organization (NACO), where screening for HIV infection is carried out routinely from different groups, namely, Volunteers (individuals opting for voluntary HIV testing), HIV-suspected cases referred from different hospitals, female sex workers (FSWs), residents at the Government Protective Home, and cases referred by District Jail and District Magistrate, Agra. The recent annual figures (Jan. through

TABLE 2. Clinical presentations and bacteriological index among the HIV-leprosy co-infected patients.

		Clinical findings				
		Skin Lesions	Nerves	Pain	Deformity	
1	BL	>5	5	Pain	Nil	Smear 3+ (Negative after 24 months)
2	BL	>5	4	Nil	Nil	Smear 2+ (Negative after 6 months)
3	BB	>5	1	Nil	Nil	Negative
4	BT	1	Nil	Nil	Nil	Negative
5	LL	>5	4	Nil	Hand	Smear 3+ (Negative after 6 months)
6	BB	1	4	Nil	Hand	Negative
7	BB	>5	6	Nil	Nil	Negative
8	BT	>5	4	Nil	Hand	Smear 3+ (Negative after 24 months)

Dec., 2004) revealed that the local prevalence and incidence of HIV-positivity in the area is, 40.31% (156/387) among Volunteers and 43.39% (46/106) among the Referred cases (communicated).

In the second phase as compared to that of the first phase, the OPD attendance of a few types of leprosy patients has risen during the study phase, whereas others have declined. A striking feature which has emerged during the second phase of the study is that there is an increase in the attendance of BB and BL types of leprosy patients, whereas there is a decrease in the BT and TT types of leprosy patients as depicted in Table 1. This could be one of the reasons for the higher HIV-positivity observed among the BB and BL cases. Another one could be attributed to the better control due to multi-drug therapy (M.D.T.) and decreased transmission of *M. leprae*, with new cases dominated by a long period of incubation, in the lepromatous leprosy cases. Although the number of leprosy patients screened for HIV infection in the second phase is less as compared to those screened during the first phase, a rise in HIV infection is disturbing since this area appears to be endemic for both the infections.

Expansion of the HIV epidemic could have a significant effect on the epidemiology of leprosy. In this study, it appears that neither of the infections precipitated the other. The incidence of downgradation, as well as reversal reactions and neuritis (both chronic and acute), was not observed among the leprosy patients. None of them devel-

oped Erythema Nodosum Leprosum (ENL) reactions. The total cases of HIV-positive leprosy patients were only thirteen in both the phases (5 in phase I, and 8 in phase II), which have been followed up very carefully and with special care. We have also observed that reversal reactions and ENL did not occur among any of the HIV-leprosy co-infected cases. If the number of cases were more, then probably one might have noted some reversal or ENL reactions. To resolve the issue, a larger study, with longer follow-up is required. Clinical manifestations of lepromatous leprosy cases might be immunologically mediated and these features could be abrogated by HIV infection.

Similarly, the HIV-positive leprosy cases did not develop either AIDS related complex (ARC) or full blown case of AIDS. None of the co-infected cases have been lost so far in the follow-up. This is the first report of a decade of HIV screening of leprosy patients in this region of the country and the longest follow-up of the largest number of HIV-leprosy co-infected cases. Other studies have reported follow-up of very less number of the co-infected cases<sup>(11,26)</sup>. The underlying mechanism by virtue of which the severity of both the diseases is lowered is not known. The infectious agents and host defences seem to have co-evolved to reach balanced states where virus and host survive. While HIV has not quite yet reached an optimal balance, tuberculosis (TB), leprosy, HBV, HCV in humans or lymphocytic choriomeningitis virus (LCMV) in mice have successfully established persistence<sup>(29)</sup>.

Although the present study does not show any association between HIV and leprosy, future study is warranted to find out the reasons for cross-protection, if any, at the genetic and molecular level.

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