The role of human T cell lymphotrophic virus type 1, hepatitis B virus and hepatitis C virus coinfections in leprosy

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Leprosy spectrum and outcome is associated with the host immune response against Mycobacterium leprae. *The role of coinfections in leprosy patients may be related to a depression of cellular immunity or amplification of inflammatory responses. Leprosy remains endemic in several regions where human T cell lymphotrophic virus type 1 (HTLV-1), hepatitis B virus (HBV) or hepatitis C virus (HCV) are also endemic. We have evaluated the evidence for the possible role of these viruses in the clinical manifestations and outcomes of leprosy. HTLV-1, HBV and HCV are associated with leprosy in some regions and institutionalization is an important risk factor for these viral coinfections. Some studies show a higher prevalence of viral coinfection in lepromatous cases. Although HBV and HCV coinfection were associated with reversal reaction in one study, there is a lack of information about the consequences of viral coinfections in leprosy. It is not known whether clinical outcomes associated with leprosy, such as development of reactions or relapses could be attributed to a specific viral coinfection. Furthermore, whether the leprosy subtype may influence the progression of the viral coinfection is unknown. All of these important and intriguing questions await prospective studies to definitively establish the actual relationship between these entities.*

Key words HTLV-1 - HBV - HCV - leprosy - leprosy reaction - Hansen's disease

The leprosy spectrum is directly associated with the host immune response to *Mycobacterium leprae* antigens, which will determine not only the clinical type of disease, but also whether the development of the leprosy reactions (LRs) will occur (Rea & Modlin 1991). Therefore besides being a chronic infection, leprosy can also be regarded as an immunological disease. The leprosy spectrum comprises at one end the tuberculoid pole where cell-mediated immunity against *M. leprae* leads to few lesions and non-contagious disease. The other pole is represented by lepromatous disease characterized by infiltrated and disseminated lesions with high bacterial load, due to host cellular anergy against Hansen's bacilli. The borderline forms are associated with unstable immunity leading to mixed and ever changing clinical manifestations (Ridley & Joplin 1966, Rea & Modlin 1991).

Several coinfections in leprosy patients (LPs) may contribute to leprosy's clinical manifestations due to interference with the host immune response, either by depressing cellular immunity or amplifying inflammatory pathways (Seghal & Sharma 1998, Motta et al. 2010). Therefore, it is possible that viral coinfections may modify leprosy outcome and could be associated with more disseminated disease or a higher incidence of LRs.

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The purpose of this review is to summarize the evidence for a role of specific viral coinfections like human T cell lymphotrophic virus type 1 (HTLV-1), hepatitis B virus (HBV) and hepatitis C virus (HCV) in leprosy.

HTLV-1 - HTLV-1, a single-stranded RNA retrovirus is endemic in several regions of the world and is the etiologic agent of severe specific diseases like adult T-cell leukaemia/lymphoma, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) and infective dermatitis (Manns et al. 1999). Additionally, HTLV-1 is associated with several clinical conditions in diverse organs (Caskey et al. 2007). The HTLV-1 infection interferes with the host immune response by infecting preferentially $CD4^+$ T-cells and also $CD8^+$ T-cells (Nagai et al. 2001).

HTLV-1 carriers have a spontaneous proliferation of peripheral blood mononuclear cells with a strong production of inflammatory cytokines like tumour necrosis factor (TNF)-α and interferon (IFN)-γ, but also produce higher levels of interleukin (IL)-4, IL-5 and IL-10 (T-helper 2 cytokines) when compared with seronegative subjects (Carvalho et al. 2001). Therefore the immune response may be impaired or exaggerated driving either immunosuppression or inflammatory pathways.

HTLV-1 coinfection in leprosy has been described since 1989 in a serologic survey conducted in Ivory Coast. Whereas the general prevalence of HTLV-1 in the adult population was 1.8%, the highest prevalence (13.7%) was observed in the 109 tested LPs (Verdier et al. 1989) (Table I). A higher prevalence of this virus was also found in LPs from the Congo and confirmed in leprosy subjects from Ivory Coast when compared with controls (9.7% vs. 1.9% and 9.9% vs. 1.5%, respectively) (Verdier et al. 1990). There was no correlation between

the clinical form of leprosy and HTLV-1 coinfection. Interestingly, another survey in Congo showed that besides a high prevalence of HTLV-1 in LPs (8.7%) the investigation of the household contacts showed a higher positivity (12.8%) for this virus (Milanga et al. 1999).

Outside Africa, Hanada et al. (1989) documented HTLV-1 coinfection in 25.8% of 525 LPs living in a highly endemic area in Japan for HTLV-1 whereas the seroprevalence of HTLV-1 in healthy controls was 11.9%. Hideroni et al. (1998) showed that leprosy subjects from two sanatoria in Japan had a higher HTLV-1 prevalence than the general Japanese population from the same regions. The authors tested 450 (sanatorium A) and 394 (sanatorium B) patients and found coinfection in 8.4% and 8.6%, respectively. The subjects were confined to sanatoria for more than 30 years and the majority came from non-endemic regions, suggesting that sexual contact and needle sharing for vaccination were the likely infection routes rather than vertical transmission. There was no association of HTLV-1 seropositivity with leprosy type and no case of HAM-TSP was described.

A study of survival of 327 leprosy inpatients in the Congo over a 22 year period showed that HTLV-1 coinfection was associated with an increased mortality rate of 5.5/100 person years compared to 3.6/100 person years in those not coinfected. The risk ratio for mortality associated with HTLV-1 was 1.4 (confidence interval: 1.04-1.89) and there was no effect of clinical type of leprosy. However no clear explanation for the higher mortality rate in the coinfected patients could be ascertained. The overall prevalence of HTLV-1 was 37% among the in-patients and 25% among the controls (Lechat et al. 1997). It could be hypothesized that the higher seropositivity for HTLV-1 found in these studies could be related to a higher antibody production by B cell hyper responsiveness in LPs and therefore not associated to HTLV-1 infection. The presence of false-positive antibodies against human immunodeficiency virus (HIV) and HTLV-1 was investigated in LPs. It was found cross-reactivities between lipoarabinomannan IgM and phenolic glycolipid-I (PGL-I) IgM and HIV-1 pol and gag proteins, but not with HTLV-1 (Kashala et al. 1994).

On the other hand, in Ethiopia a survey for HTLV-1 in LPs showed prevalence 0.4%, lower than the 0.8% rate in patients with other dermatological diseases (Tekle-Haimanot et al. 1991). Additionally a low rate (1.9%) of HTLV-1 infection was detected in 107 leprosy subjects in New York City (Glaser et al. 1994).

These apparently discordant data suggest that the association between these pathogens is stronger and more relevant in the regions that are endemic for both agents. In this context, it is presumed that the persistent HTLV-1 infection could decrease T-cell immunity and predispose to leprosy. While it is intriguing to note that although HTLV-1 modifies the host immune response and therefore may interfere with the clinical picture and evolution of leprosy, these studies did not describe any specific clinical outcomes.

HBV and HCV - HBV and HCV are major public health concern and can lead to hepatic cirrhosis and hepatocellular carcinoma. The estimated worldwide burden of chronic HBV infection is 370 million people (Alter 2006).

HBV is a DNA virus which is not directly cytopathic and persistent HBV infection is associated with impairment in early $CD4^+$ T-cell activation that induces low $CD8^+$ T-cell functional responses (Chisari et al. 2010). Therefore, patients with deficient cellular immune responses are more likely to develop chronic infections.

HCV is a single-stranded RNA virus that infects about 170 million persons worldwide. Approximately 85% of patients infected with HCV will develop chronic infection (Ashfaq et al. 2011). These patients present an HCV-specific $CD8^+$ T-cell cytotoxicity defect as well as low TNF-α and IFN-γ production (Spangenberg et al. 2005).

HBV and leprosy - The association between HBV and leprosy has been described since Blumberg et al. (1967) initially reported a higher prevalence of Australia antigen in lepromatous leprosy (LL) than in patients with tuberculoid leprosy (TT) or in non-leprosy controls, suggesting that subjects infected with HBV were susceptible to LL due to a deficient immune response.

Chiron et al. (1985) reviewed approximately 50 studies of HBV coinfection in LPs. Several studies reported a higher prevalence of HBV coinfection in the LL or in any type of LPs compared to controls while others did not confirm the association. These discordant results may be related to different degrees of endemicity of HBV infection in the study areas and several differences in methodological approach, such as use of control groups and specific HBV infection markers.

The seroprevalence of HBV markers (HBsAg, anti-HBs and anti-HBc) was compared in LL out-patients and in-patients from Central Brazil before a HBV vaccination programme (Rosa et al. 1992). The prevalence of HBV exposure was higher among institutionalized patients (64.9%) than for out-patients (22.4%) irrespective of age group, suggesting that institutionalization was a risk factor for HBV infection. Only LL cases were included and clinical outcomes were not reported, which limits any inferences about potential effects of HBV coinfection in the leprosy spectrum.

Ramos et al. (2011) studied the prevalence of HBV in 191 leprosy outpatients and found HBV exposure (anti-HBc antibodies) in 27.7%, higher than the general population of this region of Brazil (10.3%). Anti-HBs was found in 6.3% of patients, which were considered as a consequence of previous vaccination. Only 1% of these subjects were considered to be HBV carriers (HBsAg positive). The identified risk factors were the use of parenteral medications and number of sexual partners. Although the LPs had a higher prevalence of HBV exposure, this was not associated with a higher risk for development of chronic HBV infection. HBV coinfection was not associated with the clinical form of leprosy and there was no data regarding the emergence of inflammatory reactions.

HCV and leprosy - Frommel et al. (1993) described an overall seroprevalence of 2% of anti-HCV antibodies in 1,580 subjects from Ethiopia. The highest prevalence were found in LPs (3.6%) and among patients with neu-

TABLE I

Association of human T-cell lymphotrophic virus type 1 (HTLV-1) infection with leprosy

Leprosy patients total number/seropositivity n (%) - country	Control total number/seropositivity n (%)	Leprosy type/ clinical outcome	Comments	Reference
109 (13.7) - Ivory Coast	1,291 (1.8)	No data	Other groups like prostitutes (7.4%) and neurologic patients (5.8%) had lower prevalence rates.	Verdier et al. (1989)
525 (25.8) - Japan	4,741 (11.9)	No data	Other groups: strongyloidiasis (47.8%), chronic renal failure (33.8%), tuberculosis (29.5%).	Hanada et al. (1989)
1,493 (9.9) - Ivory Coast; (9.7) - Congo; (0.9) Senegal; (0) - Yemen	1,866 (1.5) - Ivory Coast; (1.9) - Congo; (0.3) Senegal; (0) - Yemen	Not related to leprosy type. No data on clinical outcomes.	Age adjusted mean prevalence was 5.6% for Congo) and 5.7% for Ivory Coast.	Verdier et al. (1990)
250 (0.4) - Ethiopia	248 (0.8) 365 (0)	No data	0.8% in dermatologic patients, 0% in the blood donor controls.	Tekle-Haimanot et al. (1991)
107 (1.9) - USA	Not done	No data	No human immunodeficiency virus coinfection.	Glaser et al. (1994)
377 (37.4) - Congo	143 (25.2)	Causes of death were not specific.	Inpatients had higher prevalence (39.6%) than outpatients (22.4%).	Lechat et al. (1997)
450 (8.4) - Sanatorium A 394 (8.6) - Sanatorium B	Not done	Not related to leprosy type. No data on clinical outcomes.	Patients were confined to sanatoria for more than 30 years.	Hideroni et al. (1998)
57 (8.7) - Congo	39 (12.8) (leprosy patients contacts)	No data	Small sample size.	Milanga et al. (1999)
199 (0) - Brazil	681 (0.15)	-	Brazil region where the study was done is not endemic for HTLV-1.	de Moraes Braga et al. (2006)

rologic disorders (6%) (Table II). The authors discuss the role of inadequate sterilization of syringes and needles as a risk factor for HCV and HIV infection among these groups of patients.

The prevalence of HCV in 1,309 LPs from seven countries (Benin, Congo, Ethiopia, Ivory Coast, Senegal, Togo and Yemen) was determined and compared to control groups using confirmatory serologic tests (Denis et al. 1994). The control group was matched by age, gender and geographical area. The HCV prevalence in the leprosy group was 7.1% vs. 2.6% in the control group. The countries with the highest rates of HCV coinfection were Yemen (21%), Congo (9.2%) and Ivory Coast (8.2%). In contrast, in the four other countries the HCV prevalence did not differ between controls and patients. The increased HCV prevalence was associated with older age and female gender. No significant differences between the leprosy clinical forms were found although LL cases had higher HCV prevalence than TT cases (9.5% vs. 4.6% respectively).

Egawa et al. (1996) tested 229 LPs from a leprosarium in Japan for markers of HCV infection. Anti-HCV antibodies were detected in 30% and HCV RNA in 18% of subjects compared to 1.2% and 1% in matched controls. This high rate of HCV coinfection likely reflects the role of institutionalization as a risk factor for HCV infection, as described above for HBV.

In Central Brazil, an association between leprosy and HCV was found in 2.4% of 83 out-patients and in 1.5% of 133 in-patients which did not differ from the HCV prevalence in blood donors (1.4%) from this region (Rosa et al. 1996). A higher HCV prevalence rate of 3.5% in 199 LPs from South Brazil was found to be associated with institutionalization and all seven coinfected patients had the LL form (de Moraes Braga et al. 2006). More recently, other investigators described a 2.6% prevalence of anti-HCV antibodies in 191 LPs in Central Brazil, but the study was limited by the low number of positive subjects, lack of a control group and the absence of a confirmatory test for HCV (Ramos et al. 2011).

A study of autopsies from a Japanese sanatorium detected HCV RNA in liver samples collected since 1940 and found an increase in the prevalence of cirrhosis of the liver and hepatocellular carcinoma in the leprosy inpatients over time (Shiogama et al. 2010).

Taken together, these data show that HCV coinfection should be evaluated at least in LPs who may be considered at higher risk like in-patients, LL cases and those living in endemic regions for HCV.

Viral coinfection and LRs - LRs are acute inflammatory episodes that may occur during the chronic course of the disease in at least 40% of cases. They are responsible for neuritis and several severe disabilities associated with leprosy (Shegal & Sharma 1998, Balagon et al. 2010). LRs require prolonged use of corticosteroids, thalidomide or immunosuppressant agents that increase the disease morbidity due to their toxicities. Therefore the prevention and early treatment of LR is of utmost importance in leprosy management.

Table II
Association of hepatitis C virus (HCV) infection with leprosy

Leprosy patients total number/seropositivity n (%) - country	Control total number/seropositivity n (%)	Leprosy type/ clinical outcome	Comments	Reference
332 (3.6) - Ethiopia	834 (0.8)	No data	Other groups: dermatological patients (1.6%), neurologic patients (6%).	Frommel et al. (1993)
1,309 (7.1) - Benin, Congo, Ethiopia, Ivory Coast, Senegal, Togo and Yemen	1,596 (2.6)	Not related to leprosy type. No data on clinical outcomes.	Highest prevalence: Yemen 21%, Congo 9.2%, Ivory Coast 8.2%.	Denis et al. (1994)
229 (30) - Japan	923 (1.2)	Lepromatous patients. No data on clinical outcomes.	HCV RNA was detected in 18% of leprosy subjects compared to 1% in controls.	Egawa et al. (1996)
216 (1.8) - Brazil	Not done	No data	Blood donors from this region have a 1.4% HCV prevalence.	Rosa et al. (1996)
199 (3.5) - Brazil	681 (0.15)	Lepromatous patients. No data about clinical outcome.	In-patients at higher risk for HCV infection.	de Moraes Braga et al. (2006)
191 (2.6) - Brazil	Not done	No data	Not conclusive	Ramos et al. (2011)

There are two types of LR: type 1 or reversal reaction (RR), which is associated with a delayed-type hypersensitivity cellular response (Th1), and type 2 or erythema nodosum leprosum (ENL), which is associated with elevated peripheral production of inflammatory cytokines (like TNF-α), immune complex deposits and neutrophil infiltration in tissues (Rea & Modlin 1991, Sarno et al. 1991, Lockwood et al. 2011).

Risk factors for development of LR include borderline form of disease, initiation of multidrug therapy, high bacillary load, stress and coinfections (Shegal & Sharma 1998, Balagon et al. 2010, Motta et al. 2011).

The role of viral coinfection in LR can be exemplified by the singular interaction between HIV and leprosy and the development of highly active antiretroviral therapy-associated immune reconstitution inflammatory syndrome (IRIS), which clinically and immunologically resembles a RR (Talhari et al. 2010, Lockwood & Lambert 2011). In these cases IRIS may reveal a subclinical leprosy due to the restoration of CD4 lymphocytes and consequent tissue infiltration and inflammation. Although it is possible that a similar pathway may occur in other viral infections, the IRIS phenomena is specifically associated to the high degree of immune suppression found in patients infected with HIV and the use of antiretroviral therapy (Müller et al. 2010, Talhari et al. 2010).

Therefore, the role of other viruses that also alter the host immune response, such as HTLV-1, HBV and HCV, as potential inducers of LR remains uncertain. Although several studies have investigated leprosy associations with HTLV-1, HBV and HCV, there is a paucity of information regarding a specific role of these coinfections as risk factors for LR.

Rego et al. (2007) have studied the HBV and HCV seroprevalence in LPs with or without RR from Salvador, Northeast Brazil. It was found that among the 55 RR patients, 3.6% were positive for anti-HBV antibodies, while 5.7% were coinfected with HCV. No evidence of HBV or HCV coinfection was found in 57 leprosy subjects without RR. These data suggests that HBV and HCV may be risk factors for development of RR and should be investigated in leprosy cases from geographic regions where these viruses are endemic.

A case report (Araújo et al. 2010) of a LP with ENL and also HAM-TSP suggests a possible interaction of a similar inflammatory pattern: ENL is associated with high TNF-α and IFN-γ systemic production (Sarno et al. 1991, Lockwood et al. 2011) as well as HAM-TSP where high TNF-α and IFN-γ are documented in serum and cerebrospinal fluid (Manns et al. 1999). It is not known whether either condition facilitates the other, but this case brings attention to an important potential clinical outcome in subjects with leprosy and HTLV-1 coinfection.

It is possible that an important risk factor for the emergence of LRs - i.e. HTLV-1, HBV, HCV, or other viral coinfection - has been neglected. It may be hypothesized that the interaction by such viruses and *M. leprae* predisposes the host to an inflammatory response against mycobacterial antigens, resulting in higher rates of LRs among these patients. Much effort should be done to verify this potential pathogenic association in leprosy. A better understanding of the role of these viruses in leprosy outcome (or *vice versa*) would provide knowledge about pathogenic pathways, including those involved with LRs. Moreover patients would benefit from an early diagnosis of viral coinfections with better clinical and preventive care for the associated conditions.

There is a lack of understanding of whether and how viral coinfections such as HTLV-1, HBV and HCV may interact with the host immunologic response and interfere with leprosy disease and outcome. Although there is a theoretical rationale that argues in favour of viral coinfections stimulating the host production of pro-inflammatory cytokines, leading to the emergence of LRs, this issue warrants more attention. On the other hand, it is possible that the depressed cellular immunity in the LL pole could predispose to a higher rate of viral coinfections and to host inability to control the virus leading to chronic infection. This remains to be proven. Adequately powered prospective studies are needed to definitively answer these intriguing questions.

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