



Published by DiscoverSys

# Interaction between leprosy and HIV infection

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## ABSTRACT

**Introduction:** Leprosy and Human Immunodeficiency Virus (HIV) infections still count as major health issues worldwide. Starting with the HIV pandemic back in the eighties, leprosy was feared to re-emerge as the HIV cases arose. Co-infections between leprosy and HIV were worried to cause an increase in leprosy cases, with worse clinical manifestation, predominantly toward the lepromatous spectrum, decrease in therapy response, and prolonged therapy period. Unlike its interaction with tuberculosis, HIV infection was turned out to not increasing nor deteriorating

the manifestation of leprosy infection. All clinical spectrum of leprosy was found in HIV infection patients without predomination of lepromatous type. Responses to leprosy Multi-Drug Therapy (MDT) regimen were also found similar between leprosy patients with or without HIV.

**Conclusion:** It is recommended to treat co-infective patients both with leprosy MDT and antiretroviral therapy. Manifestation of leprosy as a part of immune reconstitution syndrome need more attention and investigation.

**Keywords:** HIV infection, leprosy, interaction

**Cite This Article:** Sudarsa, P., Karna, R.V., Rusyati, L.M. 2018. Interaction between leprosy and HIV infection. *Bali Dermatology and Venereology Journal* 1(1): 13-15. DOI:10.15562/bdv.v1i1.4

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## INTRODUCTION

Leprosy is still an issue in global health situation. It is a chronic infection caused by ancient pathogen of *Mycobacterium leprae*.<sup>1,2</sup> In 2016, World Health Organization (WHO) record a total of 214.783 new cases of leprosy worldwide, with Indonesia contributed as the third most new cases after India and Brazil.<sup>3</sup> Most of leprosy endemic countries also have a rise in infection with *Human Immunodeficiency Virus* (HIV) and this bring a new consideration of possibilities on co-infection between leprosy and HIV.<sup>4</sup>

Co-infection with HIV bring a huge difference in natural history of another disease, particularly in disease caused by *Mycobacterium* infection. *Human Immunodeficiency Virus* infect CD-4 T-lymphocytes, which play a major role in host cellular immunity. Decrease in CD-4 T-lymphocytes will further disrupt the ability of host to counteract *mycobacterium* infection, and this is the case in co-infection between HIV and *Mycobacterium tuberculosis*.

When global pandemic of HIV infection arose, it was predicted that HIV would also increase the number of leprosy cases and bring worse clinical manifestation of this infection, just as in tuberculosis infection.<sup>4</sup> But, this thought was not proven until now. The prevalence and clinical spectrum of leprosy among HIV and non-HIV patients did not differ significantly. Leprosy reaction that mediated by immune response were also found among HIV patients and detection of leprosy as an immune

reconstitution syndrome (IRIS) should be considered in HIV patients receiving antiretroviral treatment. This phenomenon seemed paradoxical and indicated that manifestation of leprosy on HIV as activation of host immune response.<sup>4,5</sup> This review aimed to discuss the interaction between leprosy and HIV infection based on current references and considerations.

## Epidemiology of Co-Infection between Leprosy and HIV

Whether HIV increased the risk of leprosy infection cannot be concluded yet. Long period of leprosy incubation makes it difficult in doing a prospective cohort to see the incidence of leprosy in HIV population. Most of epidemiologic study concerning this issue was done by measuring the seroprevalence of HIV in already diagnosed-leprosy cohort or recently diagnosed leprosy compared to healthy controls. Few studies conducted in Africa between 1986-1998 found seroprevalence of HIV among leprosy patients varied between 0,4-33,3%.<sup>6</sup> In some countries where both HIV and leprosy was in high prevalence such as Brazil, India, and Ethiopia found there was no significant increase in incidence of co-infection between HIV and leprosy.<sup>6,7</sup> Large observational study by Sarno et al. (2008) in Brazil followed by 1.026 leprosy patients found the prevalence of HIV was 5,8%.<sup>8</sup> From these limited studies, meanwhile, it is concluded that HIV infection does not increase the risk of obtaining leprosy, and even though there was study that found an increase,

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Received: 17 April 2018  
Accepted: 5 Mei 2018  
Published: 11 May 2018

the risk of increase was relatively small and insignificant compared with the risk of infection by another mycobacterium such as *M. tuberculosis* and *M. avium* complex.<sup>4,7</sup>

### HIV Infection in Clinical Spectrum and Reaction of Leprosy

Clinical spectrum of leprosy traditionally depends on specific immunity of the host. Patient with tuberculoid leprosy has better cellular immune response against *M. leprae*, whereas patients with lepromatous leprosy do not have enough cellular immunity to *M. leprae*, but develop a higher specific antibody. Because HIV infection particularly attacks the cellular immunity of the host, at first it is thought that the co-infection between HIV and leprosy would alter the spectrum of leprosy, with more patients will fall to lepromatous leprosy group, with minimal granuloma formation and substantial amount of basil.<sup>5</sup> From recent study it is found that all type of leprosy based on clinical spectrum of Ridley and Jopling has been reported in HIV patients. These report showed that HIV was not affecting the clinical manifestation of leprosy and was not increasing the risk of lepromatous leprosy. Study by Sarno et al. found slight domination of paucibacillary leprosy in a cohort of leprosy among HIV patients, as much as 78% compared with 50,6% paucibacillary leprosy among non-HIV control group.<sup>8</sup> In this study the most common leprosy type found among HIV patients was borderline tuberculoid leprosy, with lower mean of bacterial index at the time of diagnosis. Most of the patients in this study were diagnosed with HIV first before diagnosed with leprosy, with HIV viral load were lower and CD4 counts were higher at the time of leprosy diagnosis. The histopathology of leprosy among HIV patients was also not significantly differ, with persistent granuloma formation that eventually known as granuloma paradox.<sup>7</sup> Sarno et al. also found that patient with HIV co-infection were developing more leprosy reaction compared with non-HIV group at the time of diagnosis. This immunological process underlying this phenomenon is still unclear, but it is thought that dysregulation of immune response in HIV patients or the treatment given were involved in this process. The delay of antigen clearance because of abnormal function in phagocytosis by macrophage in HIV patients may also contribute to the increase of leprosy reaction among HIV patients.<sup>4,8</sup>

### Immunology and Histopathology in Co-Infection between HIV and Leprosy

Patients with tuberculoid leprosy generally have a strong cellular immunity response toward

*M. leprae*, and histopathologically marked by a compact granuloma formation rich in lymphocytes dominated by CD-4 T cells. In contrary, lepromatous leprosy has a weak cellular immune response with the consequences of uncontrolled bacillary growth and spreading lesion. Histologically, lepromatous leprosy has a loose granuloma formation with macrophage and few lymphocytes predominantly CD-8 T cells. It turns out in HIV infection, leprosy maintain its ability to form granuloma, and there was no difference between HIV and non-HIV clinical and histopathological features.<sup>4-7</sup> Study by Sampaio et al. in Brazil found out that even in a very low CD-4 count, biopsy from leprosy skin lesion in HIV patients with tuberculoid leprosy still showed a well-preserved granuloma formation with normal infiltration of CD-4 lymphocytes.<sup>9</sup> Sampaio et al. further elucidate an expression of human leucocyte antigen (HLA)-DR on the dermis around granuloma as an evidence of local INF- $\gamma$  production. Low bacillary counts in skin biopsy further showed a functional yet effective immune response against *M. leprae* in HIV patients.<sup>9,10</sup> This result showed the effect of HIV infection might not the same all over the body, and CD-4 counts on peripheral blood might not always reflecting the number and function of the cells elsewhere.<sup>10</sup> Histopathological reaction found by Sampaio et al. indicate that patients with HIV and leprosy co-infection were able to maintain CD-4 T cells clone that specific to *M. leprae*. This situation is quite different with tuberculosis infection, in which tuberculosis infection may have a relative susceptibility to HIV. High cells turn-over in active granuloma of tuberculosis was related to high attraction of mononuclear cells from circulation and subsequently higher potency of infected cells recruitment. Whereas in leprosy granuloma, that merely less active, with less apoptotic rate and slower cells turn-over, bring a smaller risk of recruiting infected cells. Another consideration was the activity of the mononuclear cells itself. Activated cells were more likely to be infected by HIV because of the increase of chemokine co-receptor and accelerated cells life-cycle that lead to increasing of viral proliferation rate. Compared to *M. leprae*, tuberculosis has higher capacity to induce TNF- $\alpha$  secretion which has an important role in HIV infection. This makes the micro-inflammation environment of granuloma tuberculosis more conducive to infection and proliferation of HIV that granuloma in leprosy. The viral load of HIV and its immunological consequences increased sharply in tuberculosis and in turn suppressing the response of local granuloma compared within leprosy infection.<sup>5,9,10</sup>

### Leprosy Manifest as Part of IRIS

Immune reconstitution inflammatory syndrome (IRIS) is a worsening of clinical manifestation in patients with HIV infection after introduction of antiretroviral therapy because of reactivation or recovery immunologic response.<sup>5,6,11</sup> The pathogenesis of this reaction is not well understood. Some theories proposed that IRIS were affected by the difference of CD 4 count before and after initiation of therapy. Other mention about qualitative difference of phenotype expression and function of lymphocytes, for example the increase of CD-4 T cells memory that specifically recognizes antigen stimuli.<sup>11</sup> In 2003, the first leprosy case that reported IRIS manifestation in patient with HIV, and since then as much as 23 cases of leprosy as an IRIS condition was observed by Dets and Lockwood. Most of the leprosy cases as IRIS manifestation found in area with ARV access. The most commonly found was borderline tuberculoid leprosy with type 1 leprosy reaction and neuritis. One mechanism underlying this condition is the long incubation of this disease and the introduction of ARV that trigger the immunologic response which in turn exposing the clinical manifestation. The tendency of leprosy as part of IRIS manifestation are expected to be rising in line with increased access to ARV therapy.<sup>6</sup>

### Treatment of HIV- Leprosy Co-infection

Leprosy co-infected with HIV at first expected to be more difficult to treat with decrease efficacy of multi-drug therapy (MDT), longer duration of therapy, and more relapse. But for now, limited studies showed that HIV patients with leprosy are responding MDT as good as non-HIV leprosy patients. No longer duration of MDT were needed and HIV patients with leprosy has similar side effect profiles with non HIV leprosy patients.<sup>5,6</sup> Today's recommendation was to give standard MDT regime along with ARV therapy in HIV co-infected leprosy patients.<sup>12</sup> The risk of relapse in co-infected patients has not yet been concluded. Infection with HIV as a cofactor in this condition still cannot be excluded and increased awareness of HIV in leprosy relapse cases particularly in endemic HIV and leprosy region.<sup>12</sup> Co-infected patient that suffering from leprosy reaction are reported responding well with steroid and so this is still the mainstay therapy in severe leprosy reaction. But, therapy with steroid need closer monitoring because high dose or long period of steroid could increase or worsen opportunistic infection in HIV patients.<sup>5</sup>

### CONCLUSION

Limited studies has been done in Co-infection of leprosy and HIV and found some paradox and result

that contrary with previous beliefs. HIV until now was not increasing or worsening the manifestation of leprosy. All clinical spectrum and also leprosy reaction could be found in HIV patients with no different in manifestation and respond to treatment compared with non HIV group. The phenomenon of leprosy as an immunological entities such as IRIS manifestation still need further research. As both of this diseases are a major health problem, awareness and monitoring in the possibilities of this co-infection exist should be maintained.

### CONFLICT OF INTEREST

Author has no conflict of interest regarding all elements in this review.

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