Patients with active tuberculosis have increased expression of HIV coreceptors CXCR4 and CCR5 on CD4(+) T cells


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Patients with Active Tuberculosis Have Increased Expression of HIV Coreceptors CXCR4 and CCR5 on CD4+ T Cells

Nicole P. Juffermans,1* Peter Speelman,2 Annelies Verbon,1* Jan Veenstra,3 Cornelis Jie,5 Sander J. H. van Deventer,3 and Tom van der Poll1,3
1Laboratory of Experimental Internal Medicine and 2Department of Internal Medicine, Division of Infectious Diseases, Tropical Medicine, and AIDS, Academic Medical Centre, University of Amsterdam, and 3Department of Internal Medicine and Pulmonary Care, Sint Lucas Hospital, Amsterdam

Expression of human immunodeficiency virus (HIV) coreceptors CXCR4 and CCR5 was found to be elevated on CD4+ T cells (1) in blood samples obtained from patients with tuberculosis and (2) in blood samples obtained from healthy subjects and stimulated with mycobacterial lipoarabinomannan in vitro. These data suggest that the increase in HIV viremia that occurs in association with tuberculosis may result from up-regulation of CXCR4 and CCR5 on CD4+ T cells, thereby causing acceleration of HIV infection.

HIV infection is the strongest known risk factor for the development of tuberculosis (TB), and for HIV-infected patients who have a positive tuberculin skin test result, the lifetime risk of developing TB is ≳30% [1]. Concurrent infection with TB results in immune cells having enhanced susceptibility to HIV infection, which facilitates entry and replication of HIV [2, 3]. In vitro, monocytes of patients with TB are more susceptible to HIV infection [2]. Moreover, the level of virus replication is increased in HIV-infected patients who develop active TB, and it returns to a baseline level after treatment [3]. This finding is of clinical relevance, since patients with TB have an accelerated course of HIV infection. The chemokine receptors CXCR4 and CCR5 act as coreceptors for the entry of HIV into the CD4+ T cells [4]. HIV coreceptor expression correlates with enhancement of HIV entry into cells and HIV replication [5, 6].

We hypothesized that TB stimulates HIV coreceptor expression, thereby enhancing both the entry of HIV into immune cells and HIV replication. To investigate HIV coreceptor expression in association with TB, we measured expression of CXCR4 and CCR5 by means of fluorescence-activated cell sorter (FACS) analysis (1) done after whole blood samples from healthy subjects were stimulated in vitro with lipoarabinomannan (LAM; a cell wall component of Mycobacterium tuberculosis); and (2) done on whole blood samples from patients with TB.

Methods. Blood samples were obtained from 6 healthy subjects by use of a sterile collection system that consisted of a butterfly needle connected to a syringe (Becton Dickinson), and they were incubated at 37°C for 8 h. Anticoagulation was achieved using heparin (Leo Pharmaceutical Products; final concentration, 10 U/mL blood). Whole blood was added to sterile polypropylene tubes and was mixed with RPMI 1640 medium (Bio Whittaker; dilution, 1:1) to which LAM (which was mannose capped, isolated, and prepared from M. tuberculosis strain H37R) was added at a concentration of 1 μg/mL (LAM was kindly provided by Dr. J. T. Belisle, Colorado State University, Fort Collins, CO, under the provisions of National Institutes of Health contract NO1-AG-75320); it was stimulated at 37°C for 8 h. After this was done, FACS analysis was performed.

Blood samples were obtained from 8 patients (mean age ± SE, 31.9 ± 4.2 years) with active, culture-proven TB. The patients were receiving treatment at the Academic Medical Center (5 patients), the Sint Lucas Hospital (2), or the Municipal Health Center (1) in Amsterdam. Three patients with TB were HIV seropositive, and 2 were HIV seronegative; the HIV status of the remaining 3 patients was not determined. These latter 3 patients did not belong to a group with classic risk factors for HIV infection, and they had normal CD4 counts. They did not give permission for an HIV screening test to be done. Of the 8 patients, 4 had pulmonary tuberculosis and 4 had extrapulmonary tuberculosis. On each day that a patient was analyzed, 1 healthy HIV-seronegative control subject (i.e., a laboratory worker or a physician) was analyzed (8 subjects; mean age ± SE, 28.7 ± 2.0 years). After blood samples were obtained, they were immediately prepared for FACS analysis.

The blood samples were prepared for FACS analysis as follows. Erythrocytes were lysed with bicarbonate-buffered ammonium chloride solution (pH, 7.4). Leukocytes were recov-
Figure 1. Expression of HIV coreceptors CXCR4 and CCR5 on CD4+ T cells after incubation of whole blood samples with lipoarabinomannan (LAM, 1 μg/mL) for 8 h. *P<.05 versus incubation with RPMI 1640 medium.

Figure 2. Expression of HIV coreceptors CXCR4 and CCR5 on the circulating CD4+ T cells of 8 patients with active tuberculosis (TB) and 8 healthy control subjects.
our study involved relatively few patients, there are several reasons why we consider it likely that TB, rather than HIV, caused the difference in HIV coreceptor expression between patients with TB and control subjects. First, in a previous study, HIV-positive subjects without coinfection were found to have reduced expression of CXCR4 and only modestly increased expression of CCR5 on CD4+ T cells, in comparison with HIV-negative control subjects [8]. Second, the difference in CXCR4 and CCR5 expression in patients with TB and control subjects remained significant when only patients with TB who had a documented or likely HIV-negative status were analyzed (P < .05 for both receptors). Third, LAM up-regulated HIV coreceptor expression in vitro.

HIV coreceptors are considered an area of focus for HIV therapy. This study contributes to the idea that blocking CXCR4 and CCR5 may slow progression of HIV infection during concurrent infection [4].

References