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Inverse Relationship of Serum Hepcidin Levels with CD4 Cell Counts in HIV-Infected Patients Selected from an Indonesian Prospective Cohort Study

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Abstract

Background: Distortion of iron homeostasis may contribute to the pathogenesis of human immunodeficiency virus (HIV) infection and tuberculosis (TB). We studied the association of the central iron-regulatory hormone hepcidin with the severity of HIV and the association between hepcidin and other markers of iron homeostasis with development of TB.

Methods: Three groups of patients were selected from a prospective cohort of HIV-infected subjects in Bandung, Indonesia. The first group consisted of HIV-infected patients who started TB treatment more than 30 days after cohort enrollment (cases). The second group consisted of HIV-infected patients who were matched for age, gender and CD4 cell count to the cases group (matched controls). The third group consisted of HIV-infected patients with CD4 cell counts above 200 cells/mm^3 (unmatched controls). Iron parameters including hepcidin were compared using samples collected at cohort enrollment, and compared with recently published reference values for serum hepcidin.

Results: A total of 127 HIV-infected patients were included, 42 cases together with 42 matched controls and 43 unmatched controls. Patients with advanced HIV infection had elevated serum hepcidin and ferritin levels. Hepcidin levels correlated inversely with CD4 cells and hemoglobin. Cases had significantly higher hepcidin and ferritin concentrations at cohort enrollment compared to matched controls, but these differences were fully accounted for by the cases who started TB treatment between day 31 and 60 after enrollment. Hepcidin levels were not different in those with or without hepatitis C infection.

Conclusion: Iron metabolism is distorted in advanced HIV infection with CD4 cell counts correlating inversely with serum hepcidin levels. High serum hepcidin levels and hyperferritinemia were found in patients starting TB treatment shortly after cohort enrollment, suggesting that these parameters have a predictive value for development of manifest TB in HIV-infected patients.

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Introduction

Alterations in iron distribution are common in infectious diseases and many of these alterations may be attributable to actions of the iron-regulatory hormone hepcidin [1]. Hepcidin degrades the sole cellular iron exporter ferroportin leading to reduced iron absorption in the intestine and iron retention in monocytes and macrophages and the spleen [2].

Changes in iron homeostasis have been described in HIV-infected patients. Epidemiological studies have found an association between elevated iron status, HIV progression and the risk for opportunistic infections [3,4]. HIV replication involves several iron-dependent steps [5,6], and as a central determinant of macrophage iron contents, hepcidin may play a distinct role in HIV pathogenesis. Indeed, hepcidin was recently shown to increase HIV-1 transcription in cultured monocytes and T-cells by degradation of ferroportin with a secondary increase in intracellular iron [7]. Hepcidin may also be involved in two important complications of human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS). First, elevated hepcidin levels limit iron supply to the bone marrow. This may contribute to HIV-associated anemia, which is a common complication of advanced HIV infection with negative impact on clinical outcome and quality of life [8–11]. Second, hepcidin-mediated iron accumulation in macrophages may