Antiretroviral therapy in Thai adults and children with HIV-1 Infection
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Chapter 12:
Recurring thrombocytopenia associated with structured treatment interruption in patients with human immunodeficiency virus infection

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Recurring Thrombocytopenia Associated with Structured Treatment Interruption in Patients with Human Immunodeficiency Virus Infection

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In a structured treatment interruption (STI) trial, 3 of 23 patients in a CD4 cell count–guided treatment arm developed recurring thrombocytopenia associated with the interruption of antiretroviral therapy. All 3 patients had slightly low or normal platelet counts before initiating antiretroviral therapy. STI may play a role in inducing thrombocytopenia in patients with human immunodeficiency virus infection.

Thrombocytopenia is known to occur in patients with HIV infection and can present in both acute and chronic cases. Antiretroviral therapy (ART) has been shown to correct thrombocytopenia [1]. We describe 3 patients who had slightly low or normal platelet counts before the initiation of ART and who developed recurring thrombocytopenia associated with structured treatment interruptions (STIs). To our knowledge, there has been no previous report of this association.

Case reports. Three of 23 patients randomized to receive CD4 cell count–guided treatment in a trial of STI developed thrombocytopenia associated with cycles of treatment interruption. All 23 patients were enrolled in the HIV Netherlands Australia Thailand Research Collaboration (HIVNAT) 001 trial series in 1997 and received dual nucleoside reverse-transcriptase inhibitor (NRTI) therapy for 1 year followed by protease inhibitor–based HAART. Before randomization to STI, all patients had had a virus load of <50 copies/mL and a CD4 cell count of ≥350 cells/mm³ for at least 6 months. All patients received 2 NRTIs (either zidovudine and lamivudine or stavudine and didanosine) plus ritonavir-boosted saquinavir. The criteria to stop and restart administration of therapy for patients in the CD4 cell count–guided treatment arm were a CD4 cell count of 350 cells/mm³ and a 30% decrease or increase in the CD4 cell count.

Patient 1 was a 31-year-old man with platelet counts of 164 × 10³ cells/µL before the initiation of ART and 231 × 10³ cells/µL before the initiation of STI. He developed thrombocytopenia whenever ART was interrupted, with a nadir platelet count of 13 × 10³ cells/µL (figure 1A). There was no bleeding, except for excessive bruising at phlebotomy sites. He underwent bone marrow aspiration and biopsy, the results of which showed increased numbers of megakaryocytes without organ-isms, granulomas, or malignancy. Continuous HAART was resumed because of onset of thrombocytopenia, which resulted in rapid recovery of the platelet count. Platelet-associated IgG testing [2] performed after 3 months of HAART did not detect antibody.

Patient 2 was a 31-year-old man with platelet counts of 135 × 10³ cells/µL before the initiation of ART and 255 × 10³ cells/µL before the initiation of STI. He developed thrombocytopenia associated with ART interruptions, with a nadir platelet count of 62 × 10³ cells/µL (figure 1B). Before resuming ART according to protocol, his platelet count spontaneously increased to 101 × 10³ cells/µL, at which time platelet antibody was detected at a titer of 1:1. After 1 month of ART, the platelet count normalized, but platelet antibody remained detectable at a titer of 1:1. Although he had a poorly controlled seizure disorder, which resulted in injuries, there was no increased bleeding during the period of thrombocytopenia.

Patient 3 was a 53-year-old man with platelet counts of 175 × 10³ cells/µL before the initiation of ART and 282 × 10³ cells/µL before the initiation of STI. Like the first 2 patients, he had low platelet counts during ART interruption, with a nadir count of 42 × 10³ cells/µL (figure 1C). Results of platelet-associated IgG testing performed during ART interruption were negative. This patient was to resume HAART if the confirmatory platelet count was <50 × 10³ cells/µL. At a median follow-up time of 18 months after undergoing STI, the 20 remaining patients in the CD4 cell count–guided arm had not developed thrombocytopenia. Of these patients, 10 were male. Their mean platelet counts (± SD) before initiation of ART and STI were 238 ± 53 × 10³ cells/µL and

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286 ± 54 × 10⁴ cells/µL, respectively. For 16 of 20 patients, ART was resumed after the first interruption of treatment; the mean platelet count (± SD) immediately before resuming ART was 242 ± 63 × 10⁴ cells/µL.

There were 2 male Swiss patients in their mid-30s enrolled in a similar STI trial who also had thrombocytopenia after HAART interruption. In 1 patient, the platelet count before receipt of ART was normal (B. Hirschel, personal communication). There was no pre-ART platelet count in the other patient.

**Discussion.** Our 3 patients had a clear pattern of thrombocytopenia associated with STI. All were men, which is in accordance with reports in the literature demonstrating that proportionally more males than females have HIV-related thrombocytopenia; in contrast, proportionally more females than males have idiopathic thrombocytopenic purpura [3]. Although often asymptomatic, HIV-related thrombocytopenia may manifest clinically as a spectrum of mild to life-threatening hemorrhagic episodes [3–6]. Our patients were asymptomatic, except for 1 patient, who had excessive bruising at phlebotomy sites. HIV-related thrombocytopenia usually responds to ART [5, 7–9], although, in some patients, it persists in spite of HAART [10, 11]. While receiving HAART, all our patients had normal platelet counts.

Bone marrow sampling has little diagnostic utility in the investigation of afebrile HIV-infected patients with isolated thrombocytopenia, because HIV infection is usually the underlying cause [1]. This was true in 1 of our patients, for whom findings of bone marrow examination suggested increased destruction of peripheral platelets without evidence of opportunistic infections.

Platelet kinetic studies in HIV-infected patients showed brief

![Figure 1](image-url)
mean platelet life spans [12, 13], increased splenic sequestration, and ineffective delivery of viable platelets to the peripheral blood [14]. Possible causes of thrombocytopenia include HIV infection of megakaryocytes and decreased platelet production, increased peripheral destruction due to production of platelet antibody, or development of circulating immune complexes [5, 12, 15–18]. These circulating immune complexes contain platelet membrane components, glycoprotein (GP) Ila, and antiplatelet membrane IgG antibodies [16, 17]. The production of IgG platelet antibodies is likely induced by HIV, because the structure of HIV-enveloped GP120 mimics that of GPllla platelet membrane [19]. HIV-related thrombocytopenia can be present at any stage of HIV disease, but it is often associated with a high virus load [4]. Our patients did not have high virus load rebound after STI, although precise analysis of virus load kinetics was not performed.

We attempted to identify the cause of thrombocytopenia by performing platelet-associated IgG testing in the 3 patients. The results showed no correlation between low platelet counts and presence of platelet-associated IgG. Only 1 of 3 patients with thrombocytopenia had a weakly positive platelet-associated IgG level both before and after resuming ART. We were not able to perform tests for detection of antibody to GPllla, the results of which might have yielded a correlation. We did not find significant differences in age, sex, disease status, CD4 cell count before initiation of ART and STI, virus load, platelet count, and extent of viral rebound during ART interruption between patients with and patients without thrombocytopenia who underwent STI.

To our knowledge, there has been no report of thrombocytopenia associated with STI in patients with slightly low or normal platelet counts before initiation of ART and STI. Because STI will be 1 of the options for treating HIV infection in the near future, careful surveillance for thrombocytopenia is warranted.

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