Patient Report

Dilated cardiomyopathy in three HIV-infected children after initiation of antiretroviral therapy

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Various causes have been reported for HIV-related heart disease, including myocardial infection with HIV itself, opportunistic infections, and autoimmune response to viral infection. 1 – 4 Prior to the highly active antiretroviral therapy (HAART) era, dilated cardiomyopathy was described in up to 30 – 40% of AIDS patients with an estimated annual incidence of 15.9/1000. 5 This condition frequently leads to left heart dysfunction that becomes the major cause of heart failure, especially among HIV-infected children. However, after the introduction of HAART regimens, the prevalence of HIV-associated cardiomyopathy has been reduced by approximately 30%. 6, 7 Nonetheless, HAART itself, especially if the regimen includes protease inhibitors, is associated with an increase in both peripheral and coronary arterial diseases due to metabolic syndrome. 6, 7 Moreover, some patients who achieve HIV viral suppression and improved immune function may develop clinical symptoms of immune restoration disease (IRD), which constitutes an increased capacity of inflammatory reactions against both infectious and non-infectious antigens. Most infectious antigens arise from an unmasking of previously unrecognized infections or a worsening of ongoing opportunistic infections. 8, 9 Common pathogens include mycobacterium spp., cryptococcus, cytomegalovirus, and hepatitis viruses. 9, 10

In the present paper we report three cases of HIV-infected children who developed dilated cardiomyopathy after initiation of HAART while their HIV-viral load decreased and CD4 T-cells increased. We hypothesized that the dilated cardiomyopathy may be related to IRD. Clinical characteristics of the patients are given in Table 1.

Case 1

A 14-year-old HIV-infected girl with a history of cryptococcal meningitis developed dilated cardiomyopathy after 7 weeks of HAART. Before initiation of HAART her CD4 T-cell count was 4% (254 cells/μL) and her HIV-RNA level was 45 338 copies/mL. On admission she had a jugular venous distension, tachycardia, and S3 gallop, but no friction rub was found. Her liver was enlarged 6 cm below the right costal margin. At the time of the episode of dilated cardiomyalgia her CD4 T-cell count was 11% (596 cells/μL) and her HIV-RNA level was <400 copies/mL. Chest radiography showed marked cardiomegaly, pulmonary venous congestion with minimal pleural effusion. The echocardiogram showed a marked enlargement of the left atrium and left ventricle (left ventricular end diastolic size: 5.3 cm) with poor contraction of the left ventricle (Fig 1a). The ejection fraction was 22% (normal: 50 – 80%). The troponin T STAT immunoassay was negative and the creatine phosphokinase-MB (CPK-MB) level was normal. After treatment with i.v. furosemide, dobutamine and enalapril the patient gradually recovered within 2 weeks. Throughout the episode HAART was not discontinued. She also received medication for congestive heart failure, and at the 2 month and 6 month follow up, the ejection fractions were 48% and 58%, respectively.

Case 2

A 7-year-old HIV-infected boy with a history of excessive oral candidiasis developed clinical symptoms of heart failure in the third week of HAART. His CD4 T-cell count before initiation of HAART was 0% (4 cells/μL). When he developed the symptoms his CD4 T-cell counts were 1% (9 cells/μL) and 4% (57 cells/μL), his HIV-RNA levels were 108 and <50 copies/mL, at 3 and 6 weeks, respectively, after initiation of HAART. Chest radiography showed marked cardiomegaly. The echocardiogram indicated an ejection fraction of 27%, and dilated left atrium and left ventricle (left ventricular end diastolic size: 5.1 cm) (Fig 1b). The troponin T STAT immunoassay was positive at a level of 0.045 (0 – 0.009), the creatinine kinase-total was 345 U/L (0 – 195 U/L), and the CPK-MB level was 19 U/L (0 – 25 U/L). In addition, erythrocyte sedimentation rate was 42 mm/h (0 – 24 mm/h), and C-reactive protein was 15.3 mg/L (0 – 5). Myositis was ruled out due to the lack of any clinical symptoms. The patient received i.v. immunoglobulin (2 gm/kg) in addition to dobutamine and furosemide to improve the heart contraction. The serum neutralizing immunoglobulin for Coxsackie B virus type 3 was positive at 1:160 (cut-off point, <1:20). In addition, blood culture during the episode was reported later as positive for Mycobacterium kansasii.
Table 1 Dilated cardiomyopathy in three HIV-infected children after initiation of antiretroviral therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex, age</th>
<th>Previous opportunistic infection</th>
<th>Evidence of infection at episode</th>
<th>HAART regimen</th>
<th>Time to onset week</th>
<th>CD4 T-cell % † (cells/μL)</th>
<th>Viral load (copies/mL)</th>
<th>Echocardiogram</th>
<th>Ejection fraction ‡ (%)</th>
<th>Electrocardiogram</th>
<th>Treatment of congestive heart failure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, 14 years</td>
<td>Cryptococcal meningitis</td>
<td>No</td>
<td>3TC, d4T, NVP</td>
<td>7</td>
<td>4 (254)</td>
<td>11 (596)</td>
<td>45 338</td>
<td>&lt;400</td>
<td>Dilated cardiomyopathy (Fig. 1a)</td>
<td>Generalized ST-T change, inverted T in left chest leads</td>
<td>Furosemide, Dobutamine, Enalapril</td>
</tr>
<tr>
<td>2</td>
<td>M, 7 years</td>
<td>Oral candidiasis</td>
<td>Coxackie B M. kansasii</td>
<td>AZT, 3TC, EFV</td>
<td>3</td>
<td>0 (4)</td>
<td>1.4 ‖ (9, 57)</td>
<td>Not done</td>
<td>108</td>
<td>Dilated cardiomyopathy (Fig. 1b)</td>
<td>Generalized ST-T change, Low voltage in limb leads</td>
<td>IVIG, (2 mg/kg), Dobutamine, Furosemide</td>
</tr>
<tr>
<td>3</td>
<td>M, 6 months</td>
<td>CMV retinitis and colitis</td>
<td>No</td>
<td>3TC, d4T, NVP</td>
<td>6</td>
<td>11 (740)</td>
<td>30 (1,130)</td>
<td>&gt;750 000</td>
<td>262</td>
<td>Dilated cardiomyopathy (Fig. 1c)</td>
<td>ST-T change at II, III, aVF, left chest leads</td>
<td>Predisolone, (2 mg/kg), Dobutamine, Furosemide</td>
</tr>
</tbody>
</table>

In children, a CD4 T cell percentage of <15% is considered to be severe immunosuppression. †Ejection fraction 1, ejection fraction at the episode; Ejection fraction 2, ejection fraction at 2-month follow up; Ejection fraction 3. ‖At 6 month follow up; ‗at 12 month follow up; ‗at 3 and 6 weeks after initiation of antiretroviral therapy. 

3TC, lamivudine; aVF, augmented vector foot; CMV, cytomegalovirus; d4T, stavudine; EFV, efavirenz; HAART, highly active antiretroviral therapy; IVIG, i.v. immunoglobulin; NA, non-applicable; NVP, nevirapine; ST-T, ST-T segment.
He received medication for congestive heart failure as well as continued HAART. He also received clarithromycin and ethambutol for *M. kansasii* infection. His cardiac function gradually improved with an ejection fraction of 36% and 55% at 2 month and 12 month follow up.

## Case 3

A 1-year-old HIV-infected boy with a history of systemic cytomegalovirus infection (colitis, retinitis, encephalitis) developed symptoms of dilated cardiomyopathy at 6 weeks after initiation of HAART. His CD4 T-cell count prior to HAART was 11% (740 cells/μL) and his HIV-RNA level was >750 000 copies/mL. At the time of the episode his CD4 T-cell count had risen to 30% (1310 cells/μL) and his HIV-RNA level decreased to 262 copies/mL. The echocardiogram showed a markedly dilated left atrium and left ventricle with severely depressed left ventricular systolic function (ejection fraction: 30%; Fig. 1c). He received prednisolone (2 mg/kg per day), furosemide and dobutamine but his state worsened and he eventually died without re-assessment of his cardiac function. The blood culture taken when he died was positive for *Pseudomonas aeruginosa*. Post-mortem examination was not permitted.

## Discussion

We report three cases of HIV-infected children who developed clinical symptoms of dilated cardiomyopathy shortly after initiation of HAART. All patients had a CD4 T-cell count <15% and had opportunistic infections prior to and at the time of HAART. At the episode of cardiomegaly their HIV-RNA viral levels had decreased to <400 copies/mL (a decrease in the plasma HIV-RNA level by >2 log₁₀ copies/mL) and their CD4 T-cell counts had increased. They received inotropic drugs to improve cardiac function and continued on HAART. The clinical symptoms in two of the three patients improved, but one died from *P. aeruginosa* sepsis. Although there was no clear evidence for the causative organism of the cardiomyopathy and this condition has never been reported to be one of the manifestations of IRD, we propose that the three patients in the present study could have had dilated cardiomyopathy IRD. Further studies on the causes and associated factors of cardiomyopathy are needed in order to draw firmer conclusion. Because of the short onset of the dilated cardiomyopathy episode, the effect of antiretroviral therapy on coronary arterial disease was unlikely in these patients. Nevertheless, we recommend a careful cardiological evaluation of HIV-infected children both before and after initiation of HAART.

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## References

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