Exacerbation of depression associated with starting raltegravir: a report of four cases

Raltegravir is an HIV integrase inhibitor that has demonstrated excellent antiviral activity, safety and tolerability in clinical trials [1–4]. We report four cases of treatment-experienced HIV-infected patients who experienced significant exacerbation of pre-existing depression temporally related to the start of raltegravir therapy (Table 1).

Patient 1 is a 54-year-old man with a long-standing history of bipolar disorder. His HIV treatment included efavirenz since 2004, without apparent adverse psychiatric effects. On 5 June 2007, he was doing well and his bipolar disorder was stable. He discontinued enfuvirtide and started raltegravir, 400 mg twice daily, on 20 June 2007. He was seen by his family doctor on 27 June reporting increased depression. His dose of valproic acid was increased by his psychiatrist. For the next month, he was seen by his family doctor on 27 June reporting increased depression. His dose of valproic acid was increased by his psychiatrist.

Table 1. Characteristics of patients at the time of starting raltegravir.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (years)</th>
<th>Concomitant ARV regimen</th>
<th>Changes to ARV regimen</th>
<th>HIV-RNA (copies/ml)</th>
<th>CD4 cell count (cells/μl)</th>
<th>Psychiatric medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>3TC, lopinavir/rtv, atazanavir</td>
<td>Stop enfuvirtide</td>
<td>&lt;50</td>
<td>340</td>
<td>Bupropion, clonazepam, quetiapine, sotradoline, valproic acid, zopiclone</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>Tenofovir, FTC, atazanavir/rtv</td>
<td>Stop enfuvirtide</td>
<td>&lt;50</td>
<td>310</td>
<td>Bupropion, citalopram, clonazepam, quetiapine, risperidone</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>Abacavir, 3TC, nevirapine</td>
<td>Stop lopinavir/rtv, start darunavir/rtv</td>
<td>90</td>
<td>1330</td>
<td>Bupropion, clonazepam, dexamethasone, lithium carbonate, lorazepam, olanzapine, paroxetine</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>Tenofovir, FTC, lopinavir/rtv</td>
<td>Stop atazanavir, nevirapine, and stavudine</td>
<td>176</td>
<td>420</td>
<td>Amitriptyline, citalopram, olanzapine</td>
</tr>
</tbody>
</table>

3TC, lamivudine; ARV, antiretroviral; FTC, emtricitabine; rtv, ritonavir (low dose).
resolved gradually and, by 24 August 2007, he felt better. As of 14 March 2008, his mood was stable while still receiving raltegravir.

Patient 2 is a 44-year-old man diagnosed with depression and bipolar disorder in 2002. He discontinued lopinavir/ritonavir due to gastrointestinal intolerance and started raltegravir, 400 mg, and darunavir/ritonavir, 600/100 mg twice daily, on 8 November 2007. In February 2008, he reported the onset of profound depression shortly after changing his antiretrovirals. Doses of his psychiatric medications were decreased and his symptoms improved. As of 6 May 2008, he remains stable on raltegravir.

Patient 4 is a 40-year-old man with a history of depression with psychotic features. On 28 January 2008, he discontinued atazanavir, nevirapine, and stavudine because of gastrointestinal intolerance and started raltegravir, 400 mg twice daily. On 25 February 2008, he reported a depressed mood, lack of energy, lack of motivation, and feeling sad since starting raltegravir. On 10 March 2008, he had an ongoing severe depressed mood, increasing auditory hallucinations, poor sleep, lack of energy, and was irritable and angry. Citalopram was discontinued and he started venlafaxine extended release, 75 mg daily. By 31 March, he reported his depressed mood was resolved. On 26 May 2008, his depression and psychotic symptoms were stable and raltegravir was continued.

Patient 3 is a 55-year-old man diagnosed with depression and bipolar disorder in 2002. He discontinued enfuvirtide to raltegravir [5].

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Depression and other psychiatric adverse events in excess of those seen in the control arms have not been reported with raltegravir in clinical trials [1–4]; however, patients with a history of such disorders may be excluded from participation. No postmarketing reports of depression appear in the product information as of May 2008 [6]. To our knowledge, these are the first cases to describe an association between starting raltegravir and exacerbation of depression. The association is compelling in terms of the temporal association and the fact that the patients started no new drugs other than raltegravir, except one who concomitantly started darunavir (which is not known to be associated with depression) [7]. Two patients had simply replaced enfuvirtide with raltegravir, a strategy that has demonstrated virological success [5].

Of note, all patients had ongoing depression and were under treatment with antidepressants and other psychotropic medications. One potential cause of the observed psychiatric decompensation would be an as yet unidentified interaction between raltegravir and one or more of the psychotropic medications. Raltegravir is neither an inducer nor an inhibitor of cytochrome P450 3A4, and no clinically significant interactions are expected with drugs metabolized by this system, including the psychotropic medications received by these patients [6,8]; however, another mechanism may be affecting drug levels in this situation. At this time, the mechanism by which raltegravir may have contributed to the observed psychiatric decompensation remains unknown. In addition, it is not currently known whether this is a class effect of the integrase inhibitors or a specific attribute of raltegravir. Pending further study, caution and close monitoring is advised when starting raltegravir in patients with a history of depression who are currently under treatment with antidepressant and other psychotropic medications.

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References

HIV-associated anaplastic large cell lymphoma: a report of three cases

HIV-associated non–Hodgkin lymphomas recognized by the WHO lymphoma classification are mostly of B-cell origin and include Burkitt lymphoma, diffuse large B-cell lymphoma, extranodal marginal zone B-cell lymphoma, primary effusion lymphoma, plasmablastic lymphoma, classical Hodgkin lymphoma, post-transplant lymphoproliferative disorder–like polymorphic B-cell lymphoma and rarely, peripheral T-cell lymphoma [1]. T-cell lymphomas represent 3% of the lymphomas associated with HIV in a recently published series [2]. Even though at least fifteen cases of anaplastic large-cell lymphoma (ALCL) presenting in HIV patients have been reported [3–15], ALCL is not included in the WHO classification as a HIV-associated lymphoproliferative disorder.

In the present review, we report three additional cases of HIV-associated ALCL, all presenting in African–American patients with advanced extranodal disease. The clinical features, immunophenotype and molecular profile of our patients are summarized in Table 1, together with previously published cases from the literature. Interestingly, our cases were difficult to diagnose and often required extensive work up, including multiple biopsies. The CD4 cell count and viral load were markedly lowered in all our patients. In addition, these cases were negative for the human herpes virus-8 (HHV-8) and Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) positive. In addition, these cases were negative for the human herpes virus-8 (HHV-8) and Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative.

Morphologically, all three cases showed atypical large lymphocytes with abundant cytoplasm and pleomorphic nuclei with prominent nucleoli, consistent with the common variant of ALCL. They were CD30 positive, anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative, and some T cell markers positive. In addition, these cases were negative for the human herpes virus-8 (HHV-8) and Epstein–Barr virus (EBV) negative, and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative, Epstein–Barr virus (EBV) negative and some T cell markers like anaplastic lymphoma kinase (ALK) negative.

Case one presented with left thigh pain, underwent a muscle biopsy revealing atrophic muscle, and was diagnosed with pyomyositis and treated with ambulatory antibiotics. Readmission for persistence of pain and further work up, including computed tomography (CT) scans and bone marrow biopsy, showed pleural and pericardial effusions with no lymphadenopathy. A repeat open muscle biopsy established ALCL. Septicemia with Enterococcus faecalis and Mycoplasma avium was successfully treated with antimicrobials. However, rapid clinical deterioration made the patient intolerant to chemotherapy or radiation therapy, and the patient expired 1.5 months after the diagnosis.

Case two presented with sudden onset of sharp bilateral lower back pain, 15-pound weight loss, night sweats and generalized weakness for the past 2 months. A CT scan revealed multiple lytic lesions in the ribs, thoracic lumbar spine and pelvis. An infectious cause was ruled out. Ultrasound–guided core biopsies of the liver, rib and bone marrow were nondiagnostic. Finally, a laparoscopic liver wedge biopsy showed ALCL. Radiation therapy was initiated, with a plan for subsequent cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy. However, rapid clinical deterioration, including progressive nosocomial pneumonia and ileus, precluded chemotherapy, and the patient expired 1 month after the diagnosis.

Case three presented with persistent fatigue, fevers, chills and sweats. Full work up revealed ALCL involving bone marrow and lymph nodes (mediastinal and retroperitoneal). Satisfactory response to CHOP chemotherapy showed a marked decrease in lymphadenopathy and disappearance of marrow involvement. Because of adriamycin–related cardiomyopathy, doxorubicin was replaced with etoposide for the sixth cycle. Readmission for cytomegalovirus retinitis was necessary 1 month after discharge. Progressive dyspnea developed, and a CT scan demonstrated bibasilar air space disease with pleural effusions, pericardial effusion and no lymphadenopathy. Despite extensive supportive therapy, he expired in the hospital 1 year after the diagnosis.