Correspondence

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Massive hypereosinophilia and vasculitis associated with major expansion of interleukin-5-producing CD8$^+$ T cells in HIV-1 infection

We report here on a distinct form of systemic necrotizing vasculitis with extensive digital gangrene during HIV-1 infection accompanied by massive eosinophilia, and major expansion of interleukin (IL)-5-producing peripheral blood CD8$^+$ T cells with CD8$^+$ T-cell infiltration in the skin biopsy, strongly suggesting that CD8$^+$ T-cell dysregulation was involved in its pathogenesis.

A 51-year-old HIV-1-seropositive Caucasian man presented with a 3-day progressive necrosis of fingers and toes (Fig. 1a), and discrete ulcerated lesions on the face and hands, with marked eosinophilia (6830/μl), high erythrocyte sedimentation rate (80 mm), and C-reactive protein (15.6 mg/dl), as well as lymphopenia (450/μl) with severe CD4$^+$ T-cell depletion (9 cells/μl; 1.7%) and viremia of 75 000 RNA copies/ml. HIV-1 infection was diagnosed 11 years before (96 CD4$^+$ T cells/μl; 421 HIV-1 RNA copies/ml), and intermittently treated, being asymptomatic during the past 4 years without antiretroviral therapy (ART) due to patient decision. Skin biopsies of the digit lesions revealed thrombi in the dermal vessels with necrosis of the epidermis and perivascular lymphocytic infiltration (CD8$^+$) involving superficial and profound layers (Fig. 1b). There were IgM and complement in the superficial vessels, but no leucocytoclasia, IgA deposits, cytomegalovirus (PCR) or HIV (p24, immunohistochemistry) were detected. There was neither angiographic alteration of major arterial vessels nor cryoglobulinemia. Anti-neutrophil cytoplasmic autoantibodies and other autoantibodies were negative. Myelogram and bone biopsy showed a slight increase in eosinophil number, without morphological abnormalities. Other concomitant active infections were excluded, including HCV, as well as other possible causes of hypereosinophilia, including drug hypersensitivity, and intestinal and systemic parasitosis.

Eosinophilia is not rare in HIV-1 infection, but it is usually mild to moderate and not associated with tissue damage. Massive eosinophilia similar to the one observed in this case is a recognized feature of 'idiopathic' hypereosinophilic syndrome, where tissue damage occurs in association with the eosinophilia [1]. In the lymphocytic variant, there is typically an abnormal expansion of T cells producing IL-5, an important eosinophil growth factor that may underlie the eosinophilia, with identification of T-cell clones with several possible phenotypes, namely CD3$^-$CD4$^+$, CD3$^+$CD4$^-$ CD8$^-$ and CD4$^+$CD7$^-$ [1]. We identified an abnormal population of CD8$^+$ T cells producing high levels of IL-5 (38% of the CD8$^+$ T cells) in our patient, which did not concomitantly produce IL-4 (Fig. 1c), assessed as previously described [2]. Importantly, the proportion of CD8$^+$ T cells producing interferon (IFN)-γ (10% of CD8$^+$ T cells) was much below the expected levels for this disease stage, despite the documented expansion of memory-effector CD8$^+$ T cells (83.1% of the CD8$^+$ T cells), with an activated phenotype (32.2% CD38$^+$HLA-DR$^+$ within CD8$^+$ T cells) [2,3]. Hence, it is reasonable to speculate that, in the context of an atypically low frequency of interferon-γ-producing cells [2,3], HIV may drive T-cell differentiation towards an IL5-producing CD8$^+$ T-cell phenotype.

HIV-associated vasculitis can affect all types of blood vessels and covers the entire spectrum of vasculitis as described for non-HIV patients, with multifactorial pathogenic mechanisms having been proposed, including immune dysregulation caused by CD8+ T-cell expansion [4,5]. Our patient had some clinical features similar to those of HIV-associated polyarteritis nodosa-like vasculitis, although the CD8$^+$ perivascular infiltration and the massive eosinophilia with expansion of IL-5-producing CD8$^+$ T cells did not fit this diagnosis [4,5]. A case of HIV infection with marked eosinophilia and digital gangrene has previously been reported by Enelow *et al.* [6], but no immunologic investigation of IL-5-producing T cells or the phenotype of cells involved in the perivascular infiltrate was performed.

The percentage of IL-5-producing CD8$^+$ T cells and the eosinophil count rapidly decreased after introduction of ART (tenofovir/emtricitabine and lopinavir/ritonavir, based on phenotypic and genotypic tests), corticosteroids (prednisolone 1 mg/kg/day, 6 weeks), and plasmapheresis (15 sessions). This was accompanied by a clear improvement of the ischemic symptoms, although amputation of the necrotic phalanges was required. One year after stopping steroid therapy, the abnormal T-cell population was absent, and the eosinophil count remained at normal levels, with an effective control of viremia under ART, despite the poor CD4$^+$ T-cell recovery (<200 cells/μl).

In conclusion, we documented a new form of vasculitis in HIV infection that is associated with IL-5-producing CD8$^+$ T cells and clinically characterized by digital gangrene and eosinophilia. Corticosteroid therapy and plasmapheresis in conjunction with ART corrected the

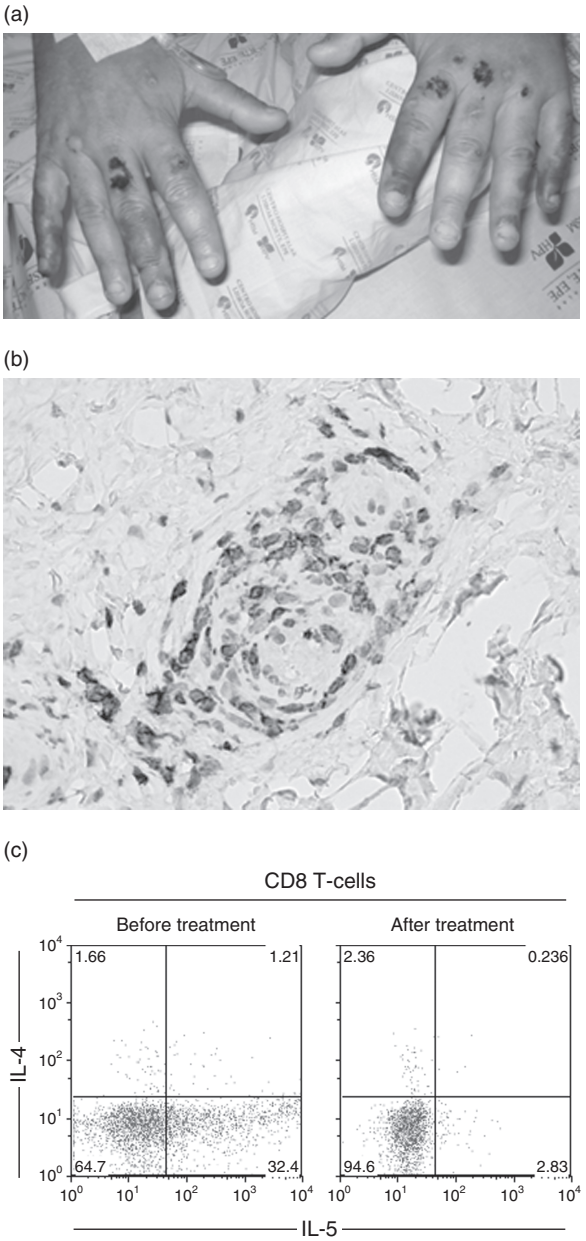

Fig. 1. Severe vasculitis associated with an expansion of interleukin (IL)-5-producing CD8$^+$ T cells in an HIV-1-infected patient. (a) Edema of the digits with necrosis of the first phalanx and intense cyanosis of the second phalanx of the third and fifth fingers of the right hand and second and fifth fingers of the left hand; discrete ulcerated lesions in the back of the hands. (b) Skin biopsy showing a vasculitic lesion with a perivascular infiltration of CD8$^+$ lymphocytes revealed by immunohistochemistry stain (×400). (c) Cytokine production by CD8$^+$ T cells before and after treatment. Freshly isolated peripheral blood mononuclear cells were stimulated for 4 h with phorbol 12-myristate 13-acetate/ionomycin in the presence of Brefeldin A. Dot plots show the proportion of cells producing both IL-5 and IL-4, or either of the two, within the CD8$^+$ T-cell population before initiation, and after 20 days of treatment.

abnormal CD8$^+$ population and the eosinophilia, concomitantly with clinical improvement. Our case justifies the increase of clinicians' awareness to this form of HIV-associated systemic vasculitis and emphasizes a role for CD8$^+$ T cells in the tissue lesions in the context of vasculitis-eosinophilic syndromes.

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Conflicts of interest

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References

1. Simon HU, Rothenberg ME, Bochner BS, Weller PF, Wardlaw AJ, Wechsler ME, *et al*. **Refining the definition of hypereosinophilic syndrome.** *J Allergy Clin Immunol* 2010; **126**:45–49.
2. Sousa AE, Chaves AF, Loureiro A, Victorino RM. **Comparison of the frequency of interleukin (IL)-2-, interferon-gamma-, and IL-4-producing T cells in 2 diseases, human immunodeficiency virus types 1 and 2, with distinct clinical outcomes.** *J Infect Dis* 2001; **184**:552–559.

3. Sousa AE, Carneiro J, Meier-Schellersheim M, Grossman Z, Victorino RM. **CD4 T cell depletion is linked directly to immune activation in the pathogenesis of HIV-1 and HIV-2 but only indirectly to the viral load.** *J Immunol* 2002; **169**:3400–3406.
4. Patel N, Khan T, Espinoza LR. **HIV infection and clinical spectrum of associated vasculitides.** *Curr Rheumatol Rep* 2011; **13**:506–512.
5. Guillevin L. **Vasculitides in the context of HIV infection.** *AIDS* 2008; **22 (Suppl 3)**:S27–33.
6. Enelow RS, Hussein M, Grant K, Cupps TR, Druckman D, Mortazavi A, *et al*. **Vasculitis with eosinophilia and digital gangrene in a patient with acquired immunodeficiency syndrome.** *J Rheumatol* 1992; **19**:1813–1816.

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Drug reaction with eosinophilia and systemic symptoms associated with raltegravir use: case report and review of the literature

Raltegravir (RAL) is the first integrase strand transfer inhibitor against HIV [1] and it is placed within first-line options in the treatment of HIV infection [2]. It is also the first agent of a new class of antivirals, which now includes two additional drugs [2], namely elvitegravir and dolutegravir.

Many pharmacological agents, including antiretrovirals [3–5], may cause a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, a potentially life-threatening drug hypersensitivity reaction, which characteristically arises after a long latency period. Due to the broad spectrum of clinical features, it may be a great mimicker of other diseases [5]. Clinical symptoms include fever, rash, lymphadenopathy, hematological abnormalities (most often eosinophilia), and involvement of at least one internal organ system (especially the liver, but also the kidneys, lungs, and heart). The mortality rate has been estimated at 10%, mostly due to liver failure [5].

Drug reaction with eosinophilia and systemic symptoms syndrome associated with RAL exposure has been rarely reported in HIV-1-infected patients [6–8]. We report a case of DRESS syndrome associated with RAL use in an African immigrant and review the literature on this topic.

A 39-year-old man from Ivory Coast was admitted to hospital in January 2013 for low-grade fever, weight loss and abdominal pain. He tested positive for HIV and his $CD4^+$ T-lymphocyte count was 3 cells/μl, HIV RNA was 4.5×10^6 copies/ml, whereas urinalysis showed a heavy proteinuria (3 g/day), interpreted as HIV-associated nephropathy. He was empirically treated for atypical mycobacteriosis with ethambutol, azytromycin, and rifabutin (blood cultures yielded *Mycobacterium avium* few weeks later) for a total of 6 months, and he was put on highly active antiretroviral therapy (HAART) (zidovudine/lamivudine + darunavir/ritonavir), along with cotrimoxazole prophylaxis. His viral load decreased to less than 50 copies/ml and $CD4^+$ cell count was 30 cells/μl at week 24 after HAART initiation.

In July 2013, he developed a symptomatic muscular toxicity (creatine phosphokinase increased to 5000 UI/l, n.v. <186 UI/l) and zidovudine/lamivudine was replaced by RAL, in the hypothesis of zidovudine-induced myopathy, whereas, for concomitant neutropenia, cotrimoxazole was switched to atovaquone.

After 4 weeks since RAL introduction, the patient developed fever with an itchy rash on the limbs and scalp, and painful oral aphthae. He was admitted to hospital in August 2013 and his blood tests showed an icteric cholestatic hepatitis and a low-grade anemia: hemoglobin (Hb) = 11.7 mg/dl, white blood cell count = 6200 cells/μl, with atypical lymphocytes and eosinophilia (560 cells/μl), aspartate aminotransferase (AST) 354 IU/l, alanine aminotransferase (ALT) 497 IU/l, total bilirubin 3.9 mg/dl, alkaline phosphatase 480 (n.v. <140). Blood smear and antigen for malaria were negative.

In the following days, the patient developed a high-grade fever (up to 39°C), associated with a sharp increase in inflammatory markers (C-reactive protein = 10.5 mg/dl, ferritin >8000 ng/ml – n.v. 250), and increased jaundice: total bilirubin rose up to 27 mg/dl, with direct bilirubin 25 mg/dl, AST 940, ALT 617 U/l, gamma-glutamyltransferase (GGT) 788 U/l (n.v. <50) and lactate dehydrogenase 2655 U/l (n.v. <460). Eosinophilia increased to 1320 cells. Chest radiograph was unremarkable and blood cultures for bacteria, fungi and mycobacteria were negative. He tested negative for hepatitis B virus and hepatitis C virus, whereas the liver biopsy showed an inflammatory infiltration, but was inconclusive. Schistocytes were absent and renal function remained normal. He also developed a severe anemia (Hb decreased to 7.4 g/dl, with normal platelet count) with a hemolytic pattern (aptoglobin fell from 127 to <5 mg/dl, direct Coombs test was positive for IgG and C3b/d at high titer), which was attributed to intravenous piperacillin/tazobactam, which the patient was receiving for a provisional diagnosis of bacterial cholecystitis (ultrasonography of the abdomen showed thickening of gall bladder wall).

In suspicion of a drug reaction, he was treated with oral prednisone (0.5 mg/kg daily) for 5 days, with a rapid improvement and a sudden relapse of symptoms at withdrawal.

He was restarted on prednisone (1 mg/kg daily), with prompt resolution of symptoms and a gradual improvement of the biochemical abnormalities. He was

Table 1. Characteristics of patients with RAL-associated DRESS syndrome.

	Patients			
	1 (current)	2 (ref. [6])	3 (ref. [7])	4 (ref. [8])
Age (years)	39	55	46	64
Ethnic group	African (Ivory Coast)	African (UK)	African (Congo)	African (Texas)
Sex	Male	Female	Female	Female
Concomitant diseases	None	type 2 diabetes mellitus, Herpes zoster	no significant medical history	hypertension, hyperlipidemia
$CD4^+$ cell count (cells/μl)	30	305	412	522
Time since starting RAL (weeks)	4	4	8	6
Fever	Yes	Yes	Yes	No
Cutaneous rash	Yes	Yes	Yes	Yes
Facial edema	No	No	No	Yes
Leucocytosis	No	Yes	No	Yes
Eosinophilia	Yes	Yes	No	Yes
Lymphadenopathy	No	No	Yes	Yes
Increased AST/ALT	Yes	Yes	Yes	Yes
Agents associated with RAL	DRV/r	ATV/r	TDF + LPV/r	DRV/r
Hospitalization	Yes	Yes	Yes	Yes
Steroid treatment	Yes	Yes	No	Yes
Outcome	Resolved	Resolved	Resolved	Resolved

DRESS, drug reaction with eosinophilia and systemic symptoms; RAL, raltegravir.

discharged home after 2 weeks, in good clinical conditions. The prednisone was tapered over 8 weeks, without recurrence of symptoms. The patient was switched to darunavir/ritonavir and abacavir/lamivudine, and, at the last follow-up visit in November 2013, he was healthy, with HIV RNA 184 copies/ml, $CD4^+$ cell count 92 cells/μl, Hb 14.6 g/dl, AST 89 U/l, ALT 111 U/l and GGT 679 U/l.

Raltegravir is likely to expand its use over the next years, both in therapy [2] and postexposure prophylaxis [9], due to its antiviral efficacy, good tolerability, low toxicity profile, and low potential for drug-to-drug interactions [1]. Recently, RAL has also been proposed in second-line options in resource-poor settings, after failing first-line non-nucleoside reverse-transcriptase inhibitor-based regimens [10].

According to a proposed scoring system for DRESS syndrome, our case scored higher than 5, confirming the diagnosis [11]. The DRESS syndrome linked to RAL has been so far described in three patients only, all of African origin, whose clinical features are summarized in Table 1 [6–8]. It is an idiosyncratic reaction to a drug and it is likely dependent on genetic factors [3]. No significant differences in any RAL pharmacokinetic parameters between African-American and white individuals have been reported [12].

The severe anemia developed in our patient was reasonably caused by piperacillin, because massive hemolysis after administration of this antibiotic has been reported in literature [13] and hemolytic anemia has not been described in DRESS syndrome [5].

In case of DRESS syndrome, RAL discontinuation is mandatory, symptoms may require longer than 2 weeks to recover and oral steroids remain commonly prescribed for several weeks, although optimum treatment is unclear [5]. Clinicians should be aware of this uncommon, but potentially fatal, adverse event associated with RAL use, particularly in African patients with advanced HIV infection, where polyfarmacy, bacterial sepsis, mycobacterial disease and immune reconstitution syndrome may be significant confounders.

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References

1. Hicks C, Gulick RM. **Raltegravir: the first HIV type 1 integrase inhibitor.** *Clin Infect Dis* 2009; **48**:931–939.
2. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/0. [Accessed Dec 2013].

3. Hetherington S, McGuirk S, Powell G, Cutrell A, Naderer O, Spreen B, *et al*. **Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir.** *Clin Ther* 2001; **23**:1603–1614.
4. Bourezane Y, Salard D, Hoen B, Vandel S, Drobacheff C, Laurent R. **DRESS (drug rash with eosinophilia and systemic symptoms) syndrome associated with nevirapine therapy.** *Clin Infect Dis* 1998; **27**:1321–1322.
5. Walsh SA, Creamer D. **Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking.** *Clin Exp Dermatol* 2011; **36**:6–11.
6. Perry ME, Almaani N, Desai N, Larbalestier N, Fox J, Chilton D. **Raltegravir-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: implications for clinical practice and patient safety.** *Int J STD AIDS* 2013; **24**:639–642.
7. Loulergue P, Mir O. **Raltegravir-induced DRESS syndrome.** *Scand J Infect Dis* 2012; **44**:802–803.
8. Zhang KS, Modi GM, Hsu S. **DRESS syndrome associated with raltegravir.** *Dermatol Online J* 2011; **17**:14.
9. Mayer KH, Mimiaga MJ, Gelman M, Grasso C. **Raltegravir, tenofovir DF, and emtricitabine for postexposure prophylaxis to prevent the sexual transmission of HIV: safety, tolerability, and adherence.** *J Acquir Immune Defic Syndr* 2012; **59**:354–359.
10. Boyd MA, Kumarasamy N, Moore CL, Nwizu C, Losso MH, Mohapi L, *et al*. **Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, noninferiority study.** *Lancet* 2013; **381**:2091–2099.
11. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, Roujeau JC. **Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist?** *Br J Dermatol* 2007; **156**:609–611.
12. Wohl DA, Dumond JB, Blevins S, Pittard D, Ragan D, Wang R, *et al*. **Raltegravir pharmacokinetics in treatment-naive patients is not influenced by race: results from the raltegravir early therapy in African-Americans living with HIV (REAL) study.** *Antimicrob Agents Chemother* 2013; **57**:784–788.
13. Mayer B, Yürek S, Salama A. **Piperacillin-induced immune hemolysis: new cases and a concise review of the literature.** *Transfusion* 2010; **50**:1135–1138.

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Reactivation of hepatitis B virus infection associated with maraviroc use in an HIV-infected patient

Maraviroc is the first CCR5 receptor antagonist for the treatment of HIV-infected patients and was approved for use in the USA in April 2007. Hepatoxocity has been reported within 1 month of starting maraviroc in a small proportion of patients, and caution has been advised when administering maraviroc to patients with pre-existing liver dysfunction or who are coinfected with either hepatitis B virus (HBV) or hepatitis C virus (HCV). However, there have been no reports of reactivation of HBV in patients treated with maraviroc.

We saw a 67-year-old man coinfected with HIV and HBV who had originally initiated antiretroviral therapy in 1994. His current regimen when presenting to our institution included tenofovir/emtricitabine, darunavir, tipranavir, ritonavir and raltegravir. His $CD4^+$ cell count was 219 cells/μl, HIV-1 RNA level 56 820 copies/ml, HBV DNA level undetectable, and hepatic transaminases were normal [AST (aspartate aminotransferase) 18 IU/l, alanine aminotransferase (ALT) 16 IU/l]. HIV genotypic resistance testing revealed pan-nucleoside/tide reverse transcriptase inhibitor resistance, as well as efavirenz, nevirapine and raltegravir resistance. A coreceptor tropism assay indicated a CCR5-tropic virus. His therapeutic regimen was adjusted to include tenofovir/emtricitabine for his chronic HBV infection, and ritonavir, darunavir, etravirine, and maraviroc at a reduced dose of 150 mg twice daily for his HIV.

Eight months after initiation of his new regimen, his $CD4^+$ cell count had risen to 287 cells/μl and HIV RNA level had fallen to 20 copies/ml. However, the patient's tranaminases had risen almost ten-fold (AST 140 IU/l, ALT 166 IU/l). HBV DNA level was elevated at 5 751 900 copies/ml. There had been no reported lapse in the patient's tenofovir/emtricitabine therapy. HBV resistance testing revealed L180M and M204V mutations predicting lamivudine resistance but not tenofovir resistance. Maraviroc was discontinued and atazanvir was added to his regimen. Over the course of the next 10 months, the patient's elevated transaminases returned to normal and his HBV DNA level once again became undetectable without the addition of a second anti-HBV agent.

In the MOTIVATE 1 and 2 trials, the incidence of grade 3 and 4 elevations in AST and ALT associated with maraviroc ranged from 3% to 4%, which was not significantly different from that found in the placebo group [1]. Only 5% of the participants in the MOTIVATE 1 trial and 7% of those in the MOTIVATE 2 trial were coinfected with hepatitis B and 8% of coinfected patients experienced a grade 2 or greater increase in ALT level [2]. There were no reports of hepatitis B reactivation in this population. Nevertheless, the prescribing information for maraviroc includes a warning that prescribers should use caution when administering maraviroc to patients who are coinfected with hepatitis B.

Maraviroc-induced HBV reactivation is theoretically possible since blockade of CCR5 receptors could diminish cell-mediated immune responses against HBV. CC ligand 3 (CCL3), CCL4 and CCL5 are three important chemokines that activate natural killer cells, macrophages and T lymphocytes through the CCR5 receptor and are required for recruitment of activated immune cells to the HBV-infected liver [3]. CCR5 receptors have also been shown to be up-regulated in HBV-specific $CD8^+$ cells from patients with chronic

hepatitis B with low levels of viremia, again suggesting that the CCR5 receptor is important in maintaining viral suppression [4].

Although an alternative explanation for the HBV reactivation could be lack of effective antiviral therapy, this is not likely in our opinion. The patient did not report any interruption in his therapeutic regimen, which is supported by the observed improvement in his HIV RNA. Furthermore, simply removing maraviroc from his regimen appears to have effectively inhibited HBV replication again. There is an ongoing study evaluating hepatic transaminase elevations in patients coinfected with HIV and either HBV and/or HCV who are receiving maraviroc [5], and changes in plasma HBV DNA levels are being monitored as a secondary outcome measure. However, this study is not estimated to be completed until mid 2015 but, hopefully, the results will shed more light on this possible association between maraviroc use and HBV reactivation.

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There are no conflicts of interest.

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References

1. Gulick RM, Lalezari J, Goodrich J, Clumeck N, DeJesus E, Horban A, *et al.*, MOTIVATE Study Teams. **Maraviroc for previously treated patients with R5 HIV-1 infection.** *N Engl J Med* 2008; **359**:1429–1441.
2. Fätkenheuer G, Nelson M, Lazzarin A, Konourina I, Hoepelman AI, Lampiris H, *et al.*, MOTIVATE 1 and MOTIVATE 2 Study Teams. **Subgroup analyses of maraviroc in previously treated R5 HIV-1 infection.** *N Engl J Med* 2008; **359**:1442–1455.
3. Ahmadabadi BN, Hassanshahi G, Khoramdelazad H, Mirzaei V, Sajadi SM, Hajghani M, *et al*. **Downregulation of CCR5 expression on the peripheral blood CD8+ T cells of southeastern Iranian patients with chronic hepatitis B infection.** *Inflammation* 2013; **36**:136–140.
4. Lee CK, Suh JH, Cho YS, Han KH, Chung JB, Chon CY, *et al*. **Chemokine receptor expression of hepatitis B virus-specific CD8+ lymphocyte in chronic B viral infection.** *Taehan Kan Hakhoe Chi* 2002; **8**:363–370.
5. A multicenter, randomized, blinded, placebo-controlled study to evaluate the safety of maraviroc in combination with other antiretroviral agents in HIV-1-infected subjects co-infected with hepatitis C and/or hepatitis B virus. ClinicalTrials.gov Identifier: NCT01327547.

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