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A new presentation of immune reconstitution inflammatory syndrome followed by a severe paradoxical reaction in an HIV-1-infected patient with tuberculous meningitis

Immune reconstitution inflammatory syndrome (IRIS) [1] is a pathological inflammatory reaction that may occur after HAART initiation in AIDS patients and target either previously treated or subclinical infections. We report the succession of an unusual acute presentation of tuberculous meningitis unmasked by antiretroviral treatment, corresponding to the first such case of IRIS, immediately followed by the onset of a severe ‘paradoxical reaction’ consisting of cerebral tuberculomas.

Case report

A 26-year-old HIV-1-seropositive woman from Guinea with a CD4 cell count of 101 cells/ μ l and a viral load of 138 100 copies/ml began antiretroviral treatment. One month later, she had a 3-day history of acute headache and vomiting revealing a meningeal syndrome. Her CD4 cell count was 258 cells/ μ l and the plasma viral load was 100 copies/ml. Magnetic resonance imaging of the brain was normal. Cerebrospinal fluid (CSF) yielded lymphocytic meningitis with a high level of protein (3 g/l) and a very low level of glucose (1.8 mmol/l); Gram and Ziehl–Neelsen stainings were negative, as were tests for herpes simplex virus, varicella zoster virus, cytomegalovirus, syphilis, and cryptococcosis. Computed tomography of the thorax and abdomen showed micronodular infiltrates of the upper lungs, low-density lesions of the spleen and liver, and multiple retroperitoneal adenopathies. She was prescribed isoniazid, rifampin, pyrazinamide, ethambutol, and intravenous steroids. Oral valgancyclovir was given for prophylaxis of cytomegalovirus infection. Antiretroviral treatment was interrupted. On day 21, CSF culture yielded a *Mycobacterium tuberculosis* isolate susceptible to all antituberculous agents. She became afebrile and her neurological status normalized. Steroids were gradually withdrawn after 7 weeks of treatment. One week later, sudden headache and homonymous lateral hemianopsia arose. Magnetic resonance imaging showed multiple tuberculomas in the optic chiasma region (Fig. 1). CSF showed a lower cell count, but persistent abnormal protein and glucose levels. Culture of CSF remained negative. Steroids and HAART were resumed; 15 months later, the patient is still on antibiotics and is well.

Three features of this case are of particular interest. Our patient had an unmasking form of IRIS as suggested by: (i) the close temporal relationship between the

introduction of HAART and the onset of meningitis; (ii) the rapid and significant immune recovery; and (iii) the unusual acute onset of tuberculous meningitis. IRIS may occur in HIV-1-infected patients starting antiretroviral treatment after an opportunistic infection [1]. The ‘unmasking variant’ of IRIS has been described as the occurrence of clinical manifestations of opportunistic infections after HAART initiation, but has not previously been reported with central nervous system tuberculosis.

The second interesting feature is the ‘paradoxical’ and uncommon [2] onset of cerebral tuberculomas during optimal treatment for meningeal tuberculosis. Such ‘paradoxical reactions’ [3] are known in HIV-seronegative patients as major inflammatory reactions at the initial site or another site of tubercular infection, and must be distinguished from relapses.

Finally, our patient is unique in the close succession of these two related but distinct immune disorders: a new presentation of IRIS, immediately followed by a severe paradoxical reaction. In immunocompetent hosts, the release of mycobacterial antigens during antituberculous treatment leads to an excessive granulomatous inflammation (paradoxical reaction), whereas the immune

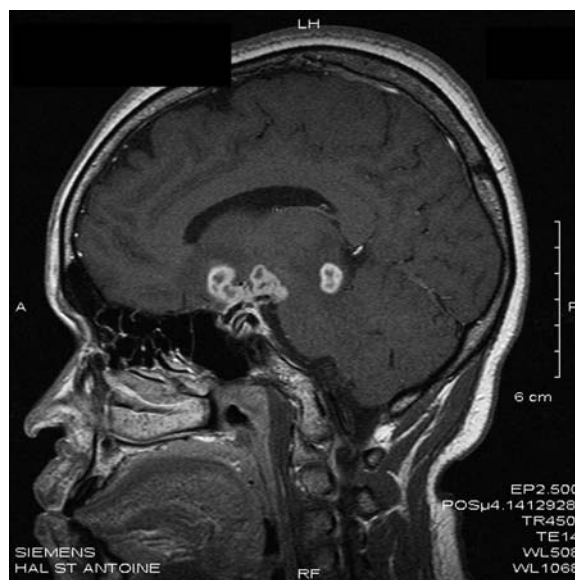


Fig. 1. Cranial magnetic resonance imaging scan, T1-weighted sequence, after gadolinium infusion, left parasagittal slice showing multiple tuberculomas in the pituitary stalk and optic chiasma region.

recovery on antiretroviral treatment in HIV patients results in a sudden inflammatory reaction against previously treated or latent pathogens, namely IRIS.

HIV-infected patients may experience severe inflammatory responses. Clinicians should be aware of the need to assess risk factors for latent tuberculosis, especially in African patients, before initiating antiretroviral treatment.

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Truvada intolerance

Nucleoside analogues remain an important backbone of antiretroviral therapy. The nucleoside backbone of emtricitabine (as Emtriva) and tenofovir (as Viread) demonstrated better tolerability than the combination of zidovudine and lamivudine (Combivir) in the Gilead 934 Study, when administered with efavirenz [1]. Truvada is a fixed-dose combination pill containing emtricitabine (200 mg) and tenofovir (300 mg). We report three patients who had gastrointestinal intolerance to Truvada but who tolerated emtricitabine or lamivudine in combination with tenofovir.

Case 1

A 58-year-old Puerto Rican woman was initially diagnosed with HIV in 1999. In 2002, she was initiated on a regimen of lamivudine, tenofovir and lopinavir/ritonavir (Kaletra), with good tolerability and CD4 cell response but persistent low-level viremia. In February 2005, she was changed to Truvada plus Kaletra to improve adherence. After initiating Truvada, she complained of nausea, heartburn, fatigue, diarrhea and epigastric pain. Truvada was stopped and lamivudine plus tenofovir restarted. Her symptoms resolved and she has continued to tolerate that regimen.

Case 2

A 52-year-old Caucasian man was diagnosed with HIV in 1996. Before 2005, he was treated with multiple protease inhibitor-based antiretroviral regimens, with poor gastrointestinal tolerance. In April 2005, he was started on Truvada, nevirapine and nelfinavir. On follow-up, he complained of nausea, bloating and epigastric gnawing

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References

1. Shelburne SA, Visnegarwala F, Darcourt J, Graviss EA, Giordano TP, White AC Jr, Hamill RJ. **Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy.** *AIDS* 2005; **19**:399–406.
2. Afghani B, Lieberman JM. **Paradoxical enlargement or development of intracranial tuberculomas during therapy: case report and review.** *Clin Infect Dis* 1994; **19**:1092–1099.
3. Breen RAM, Smith CJ, Bettinson H, Dart S, Bannister B, Johnson MA, Lipman MCI. **Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection.** *Thorax* 2004; **59**:704–707.

pain, as well as diarrhea controlled with loperamide and dietary modifications. In September 2005, Truvada was changed to emtricitabine plus tenofovir; the nausea and epigastric pain resolved thereafter, an improvement described by the patient as a 'like night and day'. He was subsequently diagnosed with and treated for *Helicobacter pylori*. He is currently tolerating a regimen of emtricitabine, tenofovir and nevirapine with a CD4 cell count of 400 cells/ μ l and a viral load under 50 copies/ml.

Case 3

A 42-year-old Haitian man was diagnosed with AIDS in 1997. *H. pylori* infection was diagnosed and treated in 1997. Multiple previous antiretroviral regimens were unsuccessful because of non-adherence, although he tolerated emtricitabine and tenofovir as part of a triple therapy in 2004. In May 2005, he started Truvada and nevirapine. Nausea and bloating occurred with the initial doses, and he stopped both medications after 4 days. In September 2005, he restarted a regimen of lamivudine, tenofovir and nevirapine, with no gastrointestinal side effects.

The three patients described above primarily had upper gastrointestinal intolerance to Truvada but all three tolerated emtricitabine (as Emtriva) or lamivudine (as Epivir) in combination with tenofovir (as Viread). An association with previous gastrointestinal symptoms or *H. pylori* infection is suggested, but in each case, symptoms resolved promptly after the discontinuation of Truvada. To our knowledge, this is the first report of this observation.

In the Gilead 934 Study, 20 of the 257 patients receiving emtricitabine (as Emtriva) plus tenofovir (as Viread) complained of mild to moderate severity nausea, but only one patient discontinued therapy [1].

Truvada was approved by the US Food and Drug Administration in 2004. Pharmacokinetic data demonstrate that Truvada is bioequivalent to emtricitabine plus tenofovir in healthy volunteers [2]. The inactive ingredients in Truvada are identical to those in Viread and Emtriva [2–4]. Each of the ingredients has been commonly used in medication formulations and is not known to induce gastrointestinal intolerance [5]. Whereas differences in the active and inactive ingredients between the individual drug formulations (Emtriva, viread) and the fixed dose combination pill (Truvada) do not suggest an obvious cause of the difference in tolerability, this remains a question for further study.

The Gilead 934 Study includes long-term follow-up, in which study participants will discontinue Emtriva plus Viread and begin Truvada. More insight into the incidence and etiology of differences in the tolerability of Truvada compared with the individual formulations awaits additional information from that study.

Successful drug treatment of immune reconstitution disease with the leukotriene receptor antagonist, montelukast: a clue to pathogenesis?

Immune reconstitution disease (IRD) is a common clinical syndrome that typically presents as symptoms developing within a few weeks of starting antiretroviral therapy [1]. The pathogenesis is not fully understood, but is thought to relate to changes in the immune response directed against local antigen [2]. Even when there is no obvious specific trigger, the symptoms can be prolonged and severe [3]. Treatment is often with steroids, which carry a degree of risk in an HIV-infected population [4]. A recent report highlighted the potential value of the leukotriene receptor antagonist, montelukast, in IRD [5]. Here we describe its use in a case of urticarial vasculitis associated with antiretroviral therapy.

A 59-year-old HIV-infected Caucasian man was started on a nucleoside-sparing regimen of saquinavir and lopinavir with ritonavir boosting 5 months after a voluntary break from treatment. Previously, he had been almost 100% adherent to therapy, and had attained an 800 cells/ μ l blood CD4 cell count increase from a nadir of 36 cells/ μ l. At the time of recommencing HAART his blood CD4 cell count, however, had declined to 226 cells/ μ l and his HIV load had risen to 34 751 viral copies/ml. He was reviewed after 3 weeks of antiretroviral treatment with a one day history of a morbilliform, urticarial rash predominantly affecting his legs, buttocks and arms (Fig. 1). His blood CD4 cell count was unchanged at 236 cells/ μ l, although his plasma viral load had reduced to 221 copies/ml.

Blood tests indicated a raised C-reactive protein (CRP) level of 79 mg/l (normal < 5 mg/l), a white cell count of

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References

1. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, et al. **Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV.** *N Engl J Med* 2006; **354**:251–260.
2. *Truvada package insert.* Foster City, California: Gilead Sciences, Inc.; March 2006.
3. *Viread package insert.* Foster City, California: Gilead Sciences, Inc.; March 2006.
4. *Emtriva package insert.* Foster City, California: Gilead Sciences, Inc.; September 2005.
5. Food and Drugs Administration. *Inactive ingredients database.* Rockville, MD: FDA; April 2006.

$20.1 \times 10^9/l$ (normal range $3.0\text{--}10.0 \times 10^9/l$) and neutrophilia of $14.7 \times 10^9/l$ ($1.5\text{--}7.4 \times 10^9/l$). Serology for syphilis, rubella, measles and parvovirus B19 demonstrated no active infection. Complement and anti-C1q antibody levels were normal and an autoimmune screen was negative. Symptomatic treatment with antihistamines (cetirizine and ranitidine) was initiated.

He was adherent to all of his medication but re-attended 2 weeks later with increasing malaise, worsening rash, fevers, diarrhoea and arthralgia. The serum CRP level was elevated at 199 mg/l, white cell count $17.2 \times 10^9/l$ and neutrophils $13.9 \times 10^9/l$. Renal function was normal. A skin biopsy revealed a perivascular inflammatory cell infiltrate with leukocytoclasia suggestive of a vasculitic process. He continued his antiretroviral drugs and was commenced on 40 mg oral prednisolone with a presumptive diagnosis of IRD-associated urticarial vasculitis. His symptoms resolved and his inflammatory markers returned to normal.

Two days after completing a total of one month's reducing steroid course, the rash and arthralgia returned associated with fever and tachycardia. Blood work again showed an acute rise in his white cell count and CRP (to 150 mg/l). He continued his antiretroviral drugs, and therapy with oral montelukast 10 mg daily was initiated. He noted an immediate improvement, and within 5 days his symptoms and signs had settled (including resolution of the increased inflammatory markers). Montelukast was discontinued after 3 months with no untoward effects. Over this time his HIV load became undetectable.



Fig. 1. Urticarial rash after 3 weeks of antiretroviral therapy.

(< 50 viral copies/ml) and his blood CD4 cell count doubled.

Although the diagnosis of IRD is currently clinical (and thus open to some overinterpretation), we believe the time course of this patient's symptoms together with the associated fall in the HIV load is consistent with IRD. He responded rapidly to treatment with steroids and subsequently with montelukast, adding to the evidence base for the use of the latter drug in the management of HIV-related IRD [5].

The pathological mechanism of IRD remains to be determined [6]. In this case of urticarial vasculitis the

dramatic effect of montelukast suggests a role for excessive leukotriene activity in its development. Leukotrienes exert broad proinflammatory effects, including leukocyte recruitment to sites of inflammation and the promotion of innate immune responses via the stimulation of cytokines and chemokines [7]. They may also be deficient in advancing HIV infection [8]. We propose that montelukast, acting as a partial agonist, attenuates an over-vigorous leukotriene-driven inflammatory response due to antiretroviral therapy without causing significant immunosuppression itself. Although one cannot yet predict who will respond to drug therapy, or the duration of treatment required, we believe that montelukast may be useful in the treatment of IRD and warrants further study.

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References

1. Shelburne SA III, Hamill RJ, Rodriguez-Barradas MC, Greenberg SB, Atmar RL, Musher DW, *et al.* **Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy.** *Medicine* 2002; **8**:213–227.
2. Lawn SD, Bekker LG, Miller RF. **Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals.** *Lancet Infect Dis* 2005; **5**:361–373.
3. French MA, Price P, Stone SF. **Immune restoration disease after antiretroviral therapy.** *AIDS* 2004; **18**:1615–1627.
4. Mayanja-Kizza H, Jones-Lopez E, Okwera A, Wallis RS, Ellner JJ, Mugerwa RD, *et al.* **Uganda—Case Western Research Collaboration. Immuno-adjunct prednisolone therapy for HIV-associated tuberculosis: a phase 2 clinical trial in Uganda.** *J Infect Dis* 2005; **191**:856–865; E-pub 8 February 2005.
5. White D, Hardwick C, Morris E, Monteiro EF, Breen RA, Lipman MCI. **Montelukast in the treatment of HIV associated immune reconstitution disease.** *Sex Trans Infect* 2006; in press.
6. Price P, Mathiot N, Kreuger R, Stone S, Keane NM, French MA. **Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy.** *J Clin Virol* 2001; **22**:279–287.
7. Peters-Golden M, Canetti C, Mancuso P, Coffey MJ. **Leukotrienes: unappreciated mediators of innate immune responses.** *J Immunol* 2005; **174**:589–594.
8. Coffey MJ, Phare SM, Kazanjian PH, Peters-Golden M. **5-Lipoxygenase metabolism in alveolar macrophages from subjects infected with the human immunodeficiency virus.** *J Immunol* 1996; **157**:393–399.

Considerations on the increase in blood pressure among antiretroviral-naïve patients starting HAART

It is currently accepted that exposure to antiretroviral therapy may increase the risk of cardiovascular disease in HIV-infected patients, although other well-known quite prevalent factors such as tobacco smoking account for

an important part of that risk [1], and the discontinuation of antiretroviral therapy is paradoxically associated with a higher risk than that of maintaining antiretroviral therapy [2]. Nevertheless, the absolute rate of myocardial

infarction in HIV-infected patients receiving antiretroviral therapy is low [3]. Although hypertension is a well-recognized risk factor for cardiovascular disease in the general population, it has not been so well studied in HIV-infected patients in whom blood pressure assessments are not routinely performed. The study by Crane *et al.* [4] offers potentially useful data on the blood pressure of HIV-infected patients initiating antiretroviral therapy. However, we believe that there are certain points concerning the methods and the interpretation of the results that need further comment.

The authors do not explain the criteria followed for the election of the antiretroviral regimen in each patient. It may be reasonable to consider that those patients more deeply immunosuppressed or those with higher plasma viral loads might have received antiretroviral regimens different from those with a better immunological and virological status. Although this is a prospective observational study, there are no longitudinal data on blood pressure assessments or the duration of exposure to individual antiretroviral drugs. It would have been useful to know the trend of changes in blood pressure after starting antiretroviral therapy and if such changes were maintained over time. The statistical analysis was performed according to the initial therapy assigned irrespective of subsequent changes. Whereas an intent-to-treat analysis is useful to assess the efficacy of antiretroviral therapy, it is arguable that the assessment of any potential adverse effect be analysed exclusively by intent to treat. It does not seem reasonable that the supposed toxicity ascribed to any drug be triggered without exposure to the potential culprit antiretroviral drug.

Regarding the assessment of blood pressure, it should be noted that current guidelines recommend performing two readings [5,6], but the authors do not mention whether they routinely followed this recommendation. The definition of outcomes indicating elevated blood pressure in the study was not standardized. A 10-mmHg increase may occur within the intrinsic variability of the assessment, and it may be irrelevant if such an increase is not sustained over time.

Some drug factors such as the use of lopinavir/ritonavir (compared with efavirenz) and tenofovir plus lamivudine (compared with zidovudine plus lamivudine) lost their significance when the increase in body mass index associated with antiretroviral therapy was also analysed. Body mass index and blood pressure are directly related in the general population [7,8], and an increase in body mass index should be expected to be associated with an increase in blood pressure. An increase in body weight (and therefore in body mass index) should be expected to occur in antiretroviral-naïve patients after several months of successful antiretroviral therapy [9,10], and some experts consider this change in weight as a 'return-to-normality' sign induced by the beneficial effects of

antiretroviral therapy [11]. Body mass index has been also identified as an independent risk factor for hypertension in HIV-infected patients in several studies [11–14]. The finding that patients with a lower CD4 cell count had a higher risk of increased blood pressure has previously been described in some [13] but not other [11,12] studies on the risk of hypertension in HIV-infected patients.

In the study by Crane *et al.* [4], most of the blood pressure values reported were normal or borderline. Therefore, antiretroviral therapy in general did not induce hypertension in most of the patients studied. Several clinical trials have been conducted with lopinavir/ritonavir and with the backbone tenofovir plus lamivudine, some of them with long-term follow-up [15,16]. In those trials, blood pressure was included among the variables routinely assessed, and there have been no reports showing a clinically significant increase in blood pressure in any of the arms studied. Because lopinavir/ritonavir (among protease inhibitors) and the combination of tenofovir plus lamivudine (among nucleoside reverse transcriptase inhibitors) have been among the most virologically potent options, it may be argued that an optimal virological effect associated with these therapies could be associated with a higher increase in body mass index in the study by Crane *et al.* [4].

In our opinion, the most important conclusions in the study by Crane *et al.* [4] should be that an increase in blood pressure associated with an increase in body mass index should be expected in HIV-infected patients starting successful antiretroviral therapy, and that such an increase does not necessarily fulfil the diagnostic criteria for hypertension. The potential long-term risk of cardiovascular disease associated with such an increase in blood pressure cannot be adequately elucidated from the study, and the potential differential effects of individual antiretroviral drugs on increasing blood pressure should not be overemphasized.

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References

1. Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, for the DAD Study Group. **Cardiovascular disease risk factors in HIV patients – association with antiretroviral therapy: results from the DAD study.** *AIDS* 2003; **17**:1179–1193.

2. El-Sadr W, Neaton J. **Episodic CD4-guided use of ART is inferior to continuous therapy: results of the SMART study.** In: *Program and abstracts of the 13th Conference on Opportunistic Infections and Retroviruses.* Denver, USA, 5–8 February 2006 [Abstract LB106].
3. Friis-Moller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, for the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. **Combination antiretroviral therapy and the risk of myocardial infarction.** *N Engl J Med* 2003; **349**:1993–2003.
4. Crane HM, Van Rompaey SE, Kitahata MM. **Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy.** *AIDS* 2006; **20**:1019–1026.
5. O'Brien E, Asmar R, Beilin L, Imai Y, Mancia G, Mengden T, for the European Society of Hypertension Working Group on Blood Pressure Monitoring. **Practice guidelines of the European Society of Hypertension for clinic, ambulatory and self blood pressure measurement.** *J Hypertens* 2005; **23**:697–701.
6. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. **Recommendations for blood pressure measurement in humans and experimental animals. Part 1: Blood pressure measurement in humans.** *Hypertension* 2005; **45**:142–161.
7. Dyer AR, Elliott P, for the INTERSALT Co-operative Research Group. **The INTERSALT study: relations of body mass index to blood pressure.** *J Hum Hypertens* 1989; **3**:299–308.
8. Brown CD, Higgins M, Donato KA, Rohde FC, Garrison R, Obarzanek E, et al. **Body mass index and the prevalence of hypertension and dyslipidemia.** *Obes Res* 2000; **8**:605–619.
9. Mallon PWG, Miller J, Cooper DA, Carr A. **Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy.** *AIDS* 2003; **17**:971–979.
10. Shlay JC, Visnegarwala F, Bartsch G, Wang J, Peng G, El-Sadr WM, et al., for the Terry Beinr Community Programs for Clinical Research on AIDS (CPCRA). **Body composition and metabolic changes in antiretroviral-naïve patients randomized to didanosine and stavudine vs. abacavir and lamivudine.** *J Acquir Immune Defic Syndr* 2005; **38**:147–155.
11. Thiébaud R, El-Sadr W, Friis-Moller N, Rickenbach M, Reiss P, D'Arminio Monforte A, et al., for the DAD Study Group. **Predictors of hypertension and changes of blood pressure in HIV-infected patients.** *Antiviral Ther* 2005; **10**:811–823.
12. Jericó C, Knobel H, Montero M, Sorli ML, Guelar A, Gimeno JL, et al. **Hypertension in HIV-infected patients: prevalence and related factors.** *Am J Hypertens* 2005; **18**:1396–1401.
13. Palacios R, Santos J, García A, Castells E, González M, Ruíz J, Márquez M. **Impact of highly active antiretroviral therapy on blood pressure in HIV-infected patients: a prospective study in a cohort of naïve patients.** *HIV Med* 2006; **7**:10–15.
14. Seaberg EC, Muñoz A, Lu M, Detels R, Margolick JB, Riddler SA, et al., for the Multicenter AIDS Cohort Study. **Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003.** *AIDS* 2005; **19**:953–960.
15. Murphy R, daSilva B, McMillan F, Hicks C, Eron J, Wolfe P, et al. **Seven year follow-up of a lopinavir/ritonavir-based regimen in antiretroviral-naïve subjects.** In: *10th European AIDS Conference.* Dublin, 17–20 November 2005 [Abstract PE7.9/3].
16. Cassetti I, Madruga JVR, Suleiman JMAH, Zhong L, Enejosa J, Cheng AK. **Tenofovir combined with lamivudine and efavirenz in antiretroviral-naïve HIV-infected patients: 4-year follow-up.** In: *3rd IAS Conference on HIV Pathogenesis and Treatment.* Rio de Janeiro, 24–27 July 2005 [Abstract WePe12.2C20].

Schistosomal colonic polyposis in an HIV-positive man

A 31-year-old Ugandan man with advanced HIV-1 disease was admitted in September 2004 with increasing breathlessness as a result of relapsed disseminated Kaposi's sarcoma causing bilateral pleural effusions. His medications were HAART; lamivudine, tenofovir and efavirenz started in November 2003; prophylactic fluconazole (for previous cryptococcal meningitis) and co-trimoxazole. His CD4 lymphocyte count was 80 cells/ μ l and his HIV viral load was less than 50 copies/ml. The left pleural effusion was drained and liposomal doxorubicin was commenced, with a significant reduction in the size of his residual effusions and good symptomatic relief. However, 15 days after admission, he developed initially watery, non-bloody diarrhoea, progressing to mucoid bloody diarrhoea.

Repeated stool examinations for ova, cysts and parasites were negative, as was culture of stool for *Campylobacter jejuni*, *Salmonella* spp., *Shigella* spp., *Vibrio* spp., *Escherichia coli* sub-type 0157 and viral culture. Electron microscopy for viral particles and cytotoxicity assays for toxin produced by *Clostridium difficile* and *Clostridium perfringens* were negative. Polymerase chain reaction for amplification of cytomegalovirus from the blood was also negative. A sigmoidoscopy revealed multiple sessile polyps, and several larger lesions that were classified as villous tumours (Fig. 1a). Biopsies were sent for histopathological examination, routine and prolonged special culture for fungi and mycobacteria. All cultures were

subsequently negative. Histopathological examination and staining of the tissue failed to show acid-fast bacilli or fungi, and no evidence of viral cytopathy or malignancy was found. However, several lesions, typical of eggs of *Schistosoma mansoni* were discovered (Fig. 1b). A diagnosis of schistosomal colonic polyposis was made. The patient was treated with two doses of praziquantel. The diarrhoea started to settle within a few weeks, and follow-up sigmoidoscopy at 3 months showed complete resolution of the lesions.

Diarrhoea is a very common symptom in HIV disease. In the era of HAART, antiretroviral drugs are a common cause [1], followed by diarrhoea of an infectious aetiology, although no cause is found in up to 46% of cases [2]. Patients in whom a diagnosis is not made by microbiological examination of the stool should proceed to endoscopy and biopsy, although even this does not always yield a diagnosis. In a case series of 103 consecutive colonic biopsies in patients with AIDS and bowel symptoms, 70% had initially been given a negative or non-specific diagnosis [3]. On re-review, one fifth of these subsequently received an alternative diagnosis.

Schistosomiasis is common, affecting 200 million people worldwide. There is a substantial geographical overlap between populations with a high incidence of HIV infection and schistosomiasis endemicity, particularly in sub-Saharan Africa. Infection with HIV-1, and decreasing

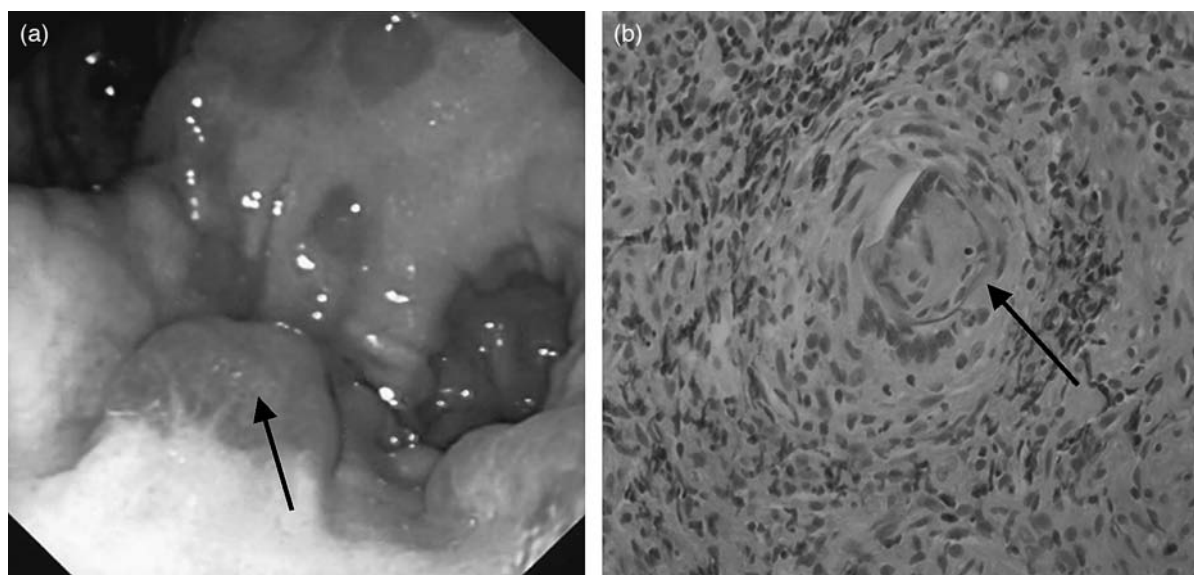


Fig. 1. Flexible sigmoidoscopy showing multiple polyps and micrograph of the biopsied polyp. (a) A particularly large polyp that was biopsied is highlighted with an arrow. (b) High power ($\times 40$) micrograph (haematoxylin and eosin stain) of the biopsied polyp seen in (a) showing a schistosome egg (arrow) with a surrounding granulomatous response.

CD4 lymphocyte counts are associated with higher infection rates by *S. mansoni* [4]. Our patient had not been in Africa for 3 years at the time of presentation, and the temporal relationship of his symptoms with the initiation of HAART several months previously suggest that his schistosomal colonic polyposis was an immune reconstitution phenomenon [5]. Gastrointestinal symptoms, although not colonic polyposis, caused by immune restoration against *S. mansoni* have recently been described [6].

Schistosomal colonic polyposis is a rare complication of infection by *S. mansoni*, which presents with bloody diarrhoea, and has been well described in Egyptian men [7]. The severity of the condition is said to correlate with egg excretion rates [7], but repeated stool examination in our patient failed to reveal schistosome eggs. Egg excretion is dependent on the immune system and is impaired in immune deficiency [8]. Some studies have reported decreased egg excretion rates in immunodeficient, HIV-infected adults [9,10], although this finding has not been replicated in all studies [11]. Praziquantel, which kills the adult worms, led to a resolution of illness indicating that there had been ongoing egg production.

To our knowledge, this is the first reported case of HIV-associated schistosomal colonic polyposis, and is further evidence of immune restoration against *S. mansoni* in the context of HIV [6,12]. In view of the treatable nature of this condition, this diagnosis should be considered in HIV-positive patients from areas endemic for schistosomiasis presenting with bloody diarrhoea of unknown cause.

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References

1. Oldfield EC III. **Evaluation of chronic diarrhea in patients with human immunodeficiency virus infection.** *Rev Gastroenterol Disord* 2002; **2**:176–188.
2. Kartalija M, Sande MA. **Diarrhea and AIDS in the era of highly active antiretroviral therapy.** *Clin Infect Dis* 1999; **28**:701–705; quiz 706–707.
3. Orenstein JM, Dieterich DT. **The histopathology of 103 consecutive colonoscopy biopsies from 82 symptomatic patients with acquired immunodeficiency syndrome: original and look-back diagnoses.** *Arch Pathol Lab Med* 2001; **125**:1042–1046.
4. Karanja DM, Hightower AW, Colley DG, Mwinzi PN, Galil K, Andove J, Secor WE. **Resistance to reinfection with *Schistosoma mansoni* in occupationally exposed adults and effect of HIV-1 co-infection on susceptibility to schistosomiasis: a longitudinal study.** *Lancet* 2002; **360**:592–596.
5. Hirsch HH, Kaufmann G, Sendi P, Battegay M. **Immune reconstitution in HIV-infected patients.** *Clin Infect Dis* 2004; **38**: 1159–1166.
6. de Silva S, Walsh J, Brown M. **Symptomatic *Schistosoma mansoni* infection as an immune restoration phenomenon in a patient receiving antiretroviral therapy.** *Clin Infect Dis* 2006; **42**:303–304.
7. el-Masry NA, Farid Z, Bassily S, Kilpatrick ME, Watten RH. **Schistosomal colonic polyposis: clinical, radiological and parasitological study.** *J Trop Med Hyg* 1986; **89**:13–17.
8. Cheever AW, Poindexter RW, Wynn TA. **Egg laying is delayed but worm fecundity is normal in SCID mice infected with *Schistosoma japonicum* and *S. mansoni* with or without recombinant tumor necrosis factor alpha treatment.** *Infect Immun* 1999; **67**:2201–2208.

9. Karanja DM, Colley DG, Nahlen BL, Ouma JH, Secor WE. **Studies on schistosomiasis in western Kenya: I Evidence for immune-facilitated excretion of schistosome eggs from patients with *Schistosoma mansoni* and human immunodeficiency virus coinfections.** *Am J Trop Med Hyg* 1997; **56**:515–521.
10. Mwanakasale V, Vounatsou P, Sukwa TY, Ziba M, Ernest A, Tanner M. **Interactions between *Schistosoma haematobium* and human immunodeficiency virus type 1: the effects of coinfection on treatment outcomes in rural Zambia.** *Am J Trop Med Hyg* 2003; **69**:420–428.
11. Kallestrup P, Zinyama R, Gomo E, Butterworth AE, van Dam GJ, Erikstrup C, Ullum H. **Schistosomiasis and HIV-1 infection in rural Zimbabwe: implications of coinfection for excretion of eggs.** *J Infect Dis* 2005; **191**:1311–1320.
12. Fernando R, Miller R. **Immune reconstitution eosinophilia due to schistosomiasis.** *Sex Transm Infect* 2002; **78**:76.

Reply to Ouattara *et al.*: past history of tuberculosis is not a risk factor for incident tuberculosis during antiretroviral treatment in South Africa

We thank Ouattara and colleagues for their letter concerning risk factors for incident tuberculosis during antiretroviral treatment (ART) in sub-Saharan Africa [1]. In a study from Abidjan that included 12 cases, Seyler *et al.* [2] identified a past history of tuberculosis as the sole risk factor for incident tuberculosis. We reported a larger number of cases ($n = 27$) within a hospital-based study cohort in Cape Town and, in contrast, a low baseline CD4 cell count and advanced World Health Organization (WHO) stage of disease were the principal risk factors [3]. In a second, much larger community-based study [4], we found that the current CD4 cell count was the sole independent risk factor for incident tuberculosis ($n = 81$). In both our studies, a history of previous tuberculosis was consistently found not to be a significant risk factor, agreeing with other unpublished studies from South Africa [5], Uganda [6] and Senegal [7]; a further study from Uganda reported a strong but statistically non-significant trend towards an association [8].

These cohorts differ in demographic characteristics, the baseline degree of immunodeficiency, socioeconomic status, the proportion of patients with previous tuberculosis treatment, exogenous tuberculosis infection pressure, and duration of follow-up. Patients with a previous history of tuberculosis may also differ with respect to tuberculosis treatment regimens received, treatment adherence, and rates of drug resistance, affecting the risk of recurrent tuberculosis. Variation between the results from different cohorts might thus be expected. However, understanding these differing findings is nevertheless important to permit the development of strategies to reduce incident tuberculosis during ART. The Abidjan data would favour isoniazid secondary prophylaxis after the completion of tuberculosis treatment. In contrast, our data suggest that the earlier initiation of ART with the maintenance of high CD4 cell counts is important or that adjunctive isoniazid prophylaxis might be used irrespective of a previous history of tuberculosis.

The suggestion of Ouattara *et al.* [1] that the data from our two studies in Cape Town are contradictory is clearly incorrect. Despite major differences in cohort characteristics, the studies were entirely consistent in finding no significant association between the risk of incident

tuberculosis and a previous history of tuberculosis [3,4]. The 95% confidence intervals around the adjusted estimates from the two studies overlap the null and do not reach statistical significance.

WHO stage is an important variable reflecting the risk of morbidity and mortality independent of that reflected by the CD4 cell count. We therefore included this variable in our analyses of tuberculosis risk. However, pulmonary and extrapulmonary tuberculosis are themselves WHO stage 3 and stage 4-defining conditions, respectively, and Ouattara and colleagues [1] question the inclusion of both the WHO stage and a history of previous tuberculosis in the same multivariate analysis. Although they overlap, these two variables reflect different information and were included separately. In our analyses, however, we found that the exclusion of one or either variables did not significantly affect the associations of the other.

WHO stage was very strongly associated with the risk of incident tuberculosis in the first of our studies [3]. The large number of incident cases in the second study, however, provided the opportunity for us to include response to ART as a potentially important additional risk factor [4]. When the current CD4 cell count (reflecting both baseline and CD4 cell response) was included in the multivariate model, then no other baseline characteristics, including WHO stage, remained significantly associated with the risk of tuberculosis [4]. The finding that alterations in tuberculosis risk parallel changes in immune function over time obviously makes biological sense; indeed, we have found that mortality risk alters in a similar way [9]. Therefore, the suggestion by Ouattara *et al.* [1] that the data from our two studies are contradictory with regard to WHO stage is again incorrect. The second of our studies builds on the findings of the first and provides a more definitive analysis.

We have previously suggested that a history of previous effective tuberculosis treatment among patients enrolling in our ART programme causes a time-dependent reduction in tuberculosis risk as a result of the sterilization of *Mycobacterium tuberculosis* infection [4,10]. Using overnight enzyme-linked immunospot assays and 7-day whole blood assays to detect *M. tuberculosis*-specific T-cell

responses, we have recently generated laboratory data that are consistent with this hypothesis (S.D. Lawn, unpublished data). Results indicate that patients enrolling for ART who do not have active tuberculosis but have previously completed tuberculosis treatment have a much lower likelihood of having viable *M. tuberculosis* infection than those who have not previously received tuberculosis treatment. Such patients would remain at a lower risk of tuberculosis until re-infected exogenously.

In summary, epidemiological data from our two study cohorts and more recent immunological studies are entirely consistent in showing that a previous history of tuberculosis is not associated with an increased risk of incident tuberculosis during ART in South Africa.

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Are a past history of tuberculosis and WHO clinical stage associated with incident tuberculosis in adults receiving antiretroviral therapy?, reply to Lawn *et al.*

In two recent excellent articles, Lawn and colleagues [1,2] reported the incidence and risk factors for active tuberculosis among HIV-infected adults receiving antiretroviral therapy (ART) in South Africa. In both studies, they found contradictory results regarding the association between the baseline World Health Organization (WHO) clinical stage and the occurrence of incident tuberculosis during follow-up, and contradictory trends towards an association between a past history of tuberculosis at enrolment and a lower (first study) or higher (second study) incidence of tuberculosis during follow-up.

We wonder if these contradictions might be a result of their multivariate analysis approach.

References

1. Ouattara E, Messou E, Gabillard D, Seyler C, Anglaret C. **Are a past history of tuberculosis and WHO clinical stage associated with incident tuberculosis in adults receiving antiretroviral therapy?** *AIDS* 2006; **20**: in press.
2. Seyler C, Toure S, Messou E, Bonard D, Gabillard D, Anglaret X. **Risk factors for active tuberculosis after antiretroviral treatment initiation in Abidjan.** *Am J Respir Crit Care Med* 2005; **172**:123–127.
3. Lawn SD, Badri M, Wood R. **Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort.** *AIDS* 2005; **19**:2109–2116.
4. Lawn SD, Myer L, Bekker LG, Wood R. **Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control.** *AIDS* 2006; **20**:1605–1612.
5. Churchyard GJ, Fielding KL, Charalambous S, Whetham J, Pemba L, Day J, Grant AD. **Antiretroviral therapy reduces risk of TB among southern African gold miners.** In: *Abstracts of the 16th International AIDS Conference*. Toronto, Canada, 13–18 August 2006 [Abstract MOPE0172].
6. Wandera B, Kigonya C, Kambugu A, Thomas D, Kamya MR. **Unmasking of mycobacteria tuberculosis in patients initiating free ARVs in an urban HIV clinic in Kampala Uganda.** In: *Abstracts of the 16th International AIDS Conference*. Toronto, Canada, 13–18 August 2006 [Abstract MOAB0105].
7. Diouf A, Etard J-F, Ndiaye I, Ngom Gueye NF, Gueye PM, Ba Fall K, *et al.* **Tuberculosis incidence and risk factors among adult patients receiving HAART in Senegal: a 7-year cohort study.** In: *Abstracts of the 16th International AIDS Conference*. Toronto, Canada, 13–18 August 2006 [Abstract MOAB0104].
8. Moore D, Ekwaru P, Liechty C, Were W, Mwima G, Solberg P, *et al.* **Prevalence, incidence and outcomes of tuberculosis treatment in HIV+ individuals initiating home-based antiretroviral therapy in rural Uganda.** In: *13th Conference on Retroviruses and Opportunistic Infections*. Denver, Colorado, USA, 5–8 February 2006 [Abstract 794].
9. Lawn SD, Myer L, Harling G, Orrell C, Bekker LG, Wood R. **Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation.** *Clin Infect Dis* 2006; **43**:770–776.
10. Lawn SD, Badri M, Wood R. **Risk factors for active tuberculosis among adults on highly active antiretroviral therapy in Africa: a reply.** *AIDS* 2006; **20**:1463–1465.

In their first study (346 patients, 14% with a past history of tuberculosis, median baseline CD4 cell count 247 cells/ μ l), Lawn and colleagues [1] used a multivariate Cox regression model to look for factors associated with incident tuberculosis. The model included sex, age, past history of tuberculosis, baseline WHO clinical stage, baseline CD4 cell count and baseline viral load as independent variables. They found that three factors were significantly associated with a higher incidence of tuberculosis after initiation of ART: having a baseline CD4 cell count of less than 100 cells/ μ l [hazard ratio (HR) 2.38, $P=0.04$], being classified at WHO clinical stage 3 or 4 (HR 3.60, $P=0.01$), or being aged under 33 years (HR 2.86, $P=0.01$). In addition, they observed a trend towards a negative association between a past

history of tuberculosis and the occurrence of incident tuberculosis, but this trend did not reach statistical significance (HR 0.31, $P=0.07$).

In their second study (944 patients, 52% with a past history of tuberculosis, median baseline CD4 cell count 96 cells/ μ l), Lawn and colleagues [2] used a multivariate Poisson regression model, including sex, age, past history of tuberculosis, baseline WHO clinical stage, prevalent tuberculosis at enrolment, current CD4 cell count, and follow-up viral load as independent variables. Of note is the fact that in that study they included in the analysis patients with prevalent tuberculosis at enrolment, but they do not clarify in their article whether a potential interaction between the 'tuberculosis past history' variable and the 'prevalent tuberculosis at enrolment' variable was looked for before including those patients in the analysis. They found that the current CD4 cell count was the only variable significantly associated with the incidence of tuberculosis after the start of ART [incidence rate ratio (IRR) 0.75 for 100 CD4 cells/ μ l increase, $P=0.007$]. In addition, they found a trend towards a positive association between a past history of tuberculosis and the occurrence of incident tuberculosis (IRR 1.46, $P=0.14$) and a trend towards a negative association between prevalent tuberculosis at enrolment and the occurrence of incident tuberculosis (IRR 0.59, $P=0.14$). Both trends were non-significant. In their second study, they did not find any significant association between the baseline WHO clinical stage and the occurrence of incident tuberculosis during follow-up.

Patients with a past history of tuberculosis are by definition classified at WHO stage 3 or 4, with the exception of patients with pulmonary tuberculosis diagnosed in more than 2 years. Therefore, including both the 'past history of tuberculosis' variable and the 'WHO clinical stage' variable in the same multivariate model of analysis for tuberculosis risk factors may lead to misleading results regarding the association of both

variables with the outcome. We suggest that further studies looking for factors associated with incident tuberculosis in patients receiving ART would combine the 'tuberculosis past history' and the 'WHO clinical stage' into one variable only, e.g. a variable with three groups: WHO stage 1 or 2; WHO stage 3 or 4 without tuberculosis past history; and WHO stage 3 or 4 with tuberculosis past history. This may help to further the still controversial issue of whether patients with a past history of tuberculosis might or might not be at a higher risk of developing active tuberculosis after the initiation of HAART [3–5].

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References

1. Lawn SD, Badri M, Wood R. **Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort.** *AIDS* 2005; **19**:2109–2116.
2. Lawn S, Myer L, Bekker L, Wood R. **Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control.** *AIDS* 2006; **20**:1605–1612.
3. Seyler C, Toure S, Messou E, Bonard D, Gabillard D, Anglaret X. **Risk factors for active tuberculosis following antiretroviral treatment initiation in Abidjan.** *Am J Respir Crit Care Med* 2005; **172**:123–127.
4. Lawn S, Badri M, Wood R. **Risk factors for tuberculosis among HIV-infected patients receiving antiretroviral treatment.** *Am J Respir Crit Care Med* 2005; **172**:1348; author reply 1348–1349.
5. Seyler C, Toure S, Messou E, Anglaret X. **Risk factors for active tuberculosis in adults on highly active antiretroviral therapy in Africa.** *AIDS* 2006; **20**:1463; author reply 1463–1465.

Conventional tuberculin skin testing versus T-cell-based assays in the diagnosis of latent tuberculosis infection in HIV-positive patients

Dheda *et al.* [1] evaluated the performance of a newly developed blood test (T-SPOT.TB) for diagnosing latent tuberculosis infection (LTBI) in HIV-infected patients. The in-vitro test detects the IFN- γ response of peripheral blood mononuclear cells (PBMC) to *Mycobacterium tuberculosis*-specific antigens (ESAT-6, CFP-10) using an enzyme-linked immunospot assay. In contrast to the conventional tuberculin skin test (TST), the new test includes a positive control based on mitogen stimulation to signal the technical reliability of the results.

In order to evaluate the performance of the T-SPOT.TB in HIV-infected individuals by impaired immune response, Dheda *et al.* [1] compared the quantitative results of the positive control reactions in HIV-negative and HIV-positive patients. In general, both groups had a similar response to the mitogen stimulation ($P=0.5$), but the response to mitogen stimulation was significantly reduced ($P=0.04$) in HIV-positive patients with a CD4 cell count less than 200 cells/ μ l. One patient had no stimulation of the positive control. Martin *et al.* [2] found

24 positive T-SPOT.*TB* tests in a cohort of 100 HIV-positive individuals with active tuberculosis or at increased risk of tuberculosis infection. They described a negative correlation between the number of ESAT-6/CFP-10 spots and the absolute CD4 cell count.

In a small study conducted by the Swiss HIV Cohort Study in Bern and St Gallen, we compared 46 HIV-positive patients from a non-endemic area (Switzerland, 76% male, median age 44 years, CD4 cells 26% lymphocytes) with 39 HIV-positive patients from a tuberculosis endemic area (sub-Saharan origin, 39% male, age 33 years, CD4 cells 23%). In both groups the conventional TST (Tuberculin PPD RT 23; Pro Vaccine, Baar, Switzerland) and the new T-SPOT.*TB* (Oxford Immunotec, Oxford, UK) were performed.

Eight T-SPOT.*TB*-tests (9.4%) were indeterminate with an insufficient positive control [≤ 20 spot-forming cells (SFC)/250 000 PBMC, range 1–15], all of them showed a negative TST result. Seven patients had a CD4 cell count greater than 200 cells/ μl , and mean CD4 cell counts from all eight patients did not differ from patients with a valid positive control (451 versus 433 cells/ μl ; $P=0.75$).

We found no significant correlation between the CD4 cell count and positivity in mitogen stimulation. The median mitogen-stimulated SFC in patients with a CD4 cell count of less than 200 cells/ μl was 347 SFC/ 10^6 PBMC versus 503 SFC/ 10^6 PBMC in patients with a CD4 cell count greater than 200 cells/ μl ($P=0.27$; Fig. 1).

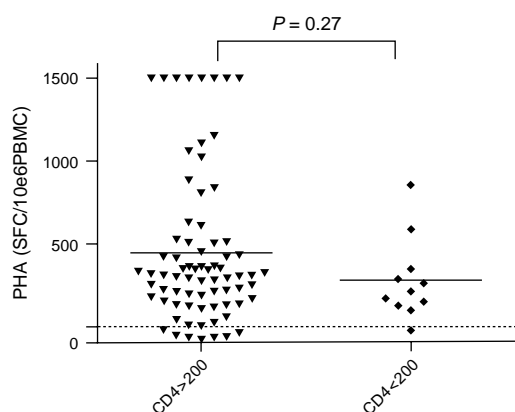


Fig. 1. Mitogen (phytohaemagglutinin) responses in HIV-infected individuals stratified by absolute CD4 cell count. The magnitude of spot-forming cells after the mitogen stimulation in HIV-positive individuals with an absolute CD4 cell count of less than 200 cells/ μl compared with individuals with a CD4 cell count greater than 200 cells/ μl . We did not find significantly different responses in the two groups. Groups were compared using the Mann–Whitney U-test. PBMC, Peripheral blood mononuclear cell; PHA, phytohaemagglutinin; SFC, spot-forming cell.

None of the 40 Swiss patients (0%) tested positive by T-SPOT.*TB* or TST, whereas nine of the 37 eligible T-SPOT.*TB* (24%) were positive in the group with a high probability of previous tuberculosis exposure. In five patients from the latter group (14%) the TST was also positive (above 5 mm). The inter-test agreement by kappa statistic was $\kappa=0.69$. We did not find a significant correlation between the ESAT-6 or CFP-10 spot numbers per 10^6 PBMC and the absolute CD4 cell count. Individuals with positive test results in both tests had a significantly higher absolute CD4 cell count than individuals with a positive T-SPOT.*TB* and negative TST ($P=0.014$).

The main problem with evaluating a new diagnostic procedure for LTBI diagnosis is the lack of a gold standard. TST can yield false-positive results in bacillus Calmette–Guérin-vaccinated patients. In HIV-infected individuals, skin anergy can reduce the sensitivity of TST in latently infected individuals. We therefore decided to use lifetime exposure to tuberculosis in an endemic area as a proxy for LTBI. Previous studies found a prevalence of LTBI in individuals from sub-Saharan Africa of 35% [3]. When historic prevalence rates were used as a gold standard, the sensitivity of the new T-cell-based assay was 70% compared with 40% for the conventional TST. Our data therefore suggest a higher sensitivity and more accurate diagnosis of LTBI in HIV-infected patients by the T-SPOT.*TB* than the conventional TST.

In contrast to Dheda *et al.* [1] we found a higher rate of indeterminate test results (9 versus 3%). In these cases the differentiation between anergic T-SPOT.*TB* results and technical failures is difficult. In our experience, indeterminate results were not associated with CD4 cell count, making a biological basis for the failures less likely.

Our results support the conclusion of Dheda *et al.* [1] and Martin *et al.* [2] that a T-cell-based assay is sensitive enough to detect LTBI in even immunocompromised patients with HIV infection. Our study confirms the good test performance in patients with low CD4 cell counts.

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Scaling up HAART in Mexico. Response to Volkow *et al.*

We appreciate the careful review of our paper [1] by Dr Volkow and her co-authors. We agree with some points they make and would like to provide some additional clarifications regarding others.

The period evaluated in our study, 1997–2001 is not, according to Dr Volkow, adequate to evaluate the rapid scaling up of treatment in Mexico, because the real scale-up access occurred only after 2000.

We not only agree with Dr Volkow, but highlight this fact in the paper. For example, in the introduction section: ‘There have been major efforts to improve access since 2001, thus the data presented here do not necessarily reflect the current standard of care for people living with HIV/AIDS in Mexico.’

Even although the period analysed in our study is before the official commitment to achieve universal access, the data reveal an impressive expansion of antiretroviral treatment during the period of observation, as reflected in the number of patients receiving any antiretroviral drugs and the number receiving triple therapy. We thus believe that this early period also merits analysis.

Dr Volkow argues that in the period evaluated, access to antiretroviral drugs was very limited, and in that context changes in treatment regimens were driven by accessibility more than prescription decisions.

We agree that interruptions in drug supply are a potentially important factor in explaining the pattern of care we observed. It was never our intention to imply any definite causality between the possible explanatory factors and the observed outcomes. We do not know and

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References

1. Dheda K, Lalvani A, Miller RF, Scott G, Booth H, Johnson MA, *et al.* **Performance of a T-cell-based diagnostic test for tuberculosis infection in HIV-infected individuals is independent of CD4 cell count.** *AIDS* 2005; **19**:2038–2041.
2. Martin S, Clark S, Dunning J, Ward B, Low E, Henderson DC, *et al.* **Utility of an antigen-specific interferon- γ assay for the detection of tuberculosis (TB) in patients with HIV-1 infection.** *HIV Med* 2006; **7** (Suppl. 1):16 [Abstract no. P23].
3. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC, for the WHO Global Surveillance and Monitoring Project. **Global burden of tuberculosis. estimated incidence, prevalence, and mortality by country.** *JAMA* 1999; **282**:677–686.

cannot know the reasons behind the observed heterogeneity in the antiretroviral treatment received by the patients in our study. Besides deficiencies in physician training, we discussed additional possibilities: ‘There are a number of other factors which can be related to suboptimal standard of care in Mexico. Interruption in drug supply is one crucial issue which could explain some of the results encountered in this study. Patients having to buy their medications and laboratory tests could be a significant factor in Mexico’s experience before 2002.’

However, the main conclusion of our paper is that scaling up of treatment in any country must consider all the potential factors that could lead to results similar to those observed, in order to avoid them. Ensuring an uninterrupted drug supply and appropriate training and monitoring of prescription practices are surely among the most important determinants of success to be considered by any country.

Dr Volkow points out that there are probably errors of misclassification of non-recommended regimes, because we used 2000 guidelines to classify treatment combinations prescribed between 1997 and 2001.

This is a fair criticism, and we agree that it would have improved the paper had we used the earlier guidelines for the initial years. That said, we do not believe that the change would significantly affect the conclusions. The total number of observations in our sample is 8363, of which 73.7% are documented in the years 2000 and 2001. The potential misclassification thus only affects a quarter of the sample. We would also argue that pre-2000 regimens that are consistent with post-2000 guidelines also be considered appropriate, suggesting that the only

relevant misclassifications are those regimens pre-2000 that are consistent with the pre-2000 guidelines and not with the post-2000 guidelines.

It was not clear for Dr Volkow how the levels of adherence were calculated in the 'observed scenario'. In addition, she argues that the approach to estimating adherence is questionable and invalidates any conclusion, given that the source of data was a retrospective review of clinical charts, which most likely will under-register patient adherence.

A truly accurate retrospective measurement of adherence levels is impossible in our setting. We explicitly acknowledge this limitation in the paper and address it in several ways. The first is by constructing several different adherence scenarios. The base scenario counted as adherent months only 'chart confirmed months of medications supplied to patients...'; the other two are more optimistic, including one with perfect adherence. Our principal conclusions are related to prescription practices, i.e. the number of changes of antiretroviral regimens, the number of non-recommended regimens, and the inefficiency of such practices. We also argue in the paper that a serious adherence problem probably exists. The fact that there was so little documentation in the records of efforts to promote, evaluate and document adherence suggests serious problems with quality of care, even if it does underestimate true adherence in the base scenario.

Dr Volkow suggests that our study did not consider differences in physicians' experience and training in our analysis.

We are not completely sure what she means by the comment. If she means to suggest that physicians with better training and more experience provided better patient care then we would agree, at least intuitively, and this is reflected in our study. We did not document physician characteristics and thus we can only hypothesize, as she does, that physician training and experience is probably an important determinant of quality care.

Reactivation of hepatitis B virus replication during peginterferon-ribavirin therapy in an HIV/hepatitis C virus-co-infected patient with isolated anti-hepatitis B core antibodies

In a recent French national survey the prevalence of isolated anti-hepatitis B core (HBc) antibodies was estimated to be 37.6% among HIV-infected patients [1]. It may be more frequent in individuals with hepatitis C virus (HCV) co-infection [2]. However, in HIV-seronegative patients with an 'anti-HBc alone' serological pattern, hepatitis B virus (HBV) DNA is detected in approximately 10% of cases and reactivation is rare [3]. In

Most importantly, Dr Volkow and her colleagues are most concerned that our paper might be used as an excuse for policy makers to back off from commitments to expand and maintain coverage. Given other publications by our group [2,3] and work to promote universal access globally to care, it is clear that this was not our intent. The authors include an apparent quote from our paper in their letter 'it is better not to treat, than to treat badly', which we cannot find in our text. What we do say is 'Such high levels of non-adherence suggest that a significant proportion of patients were receiving no benefit from their treatment and may have been better off with no ART until the system is able to ensure better adherence.' Our desire is not to give anyone an excuse for backing away from their commitments, but rather to point out that the expansion of coverage that only tracks the number of patients receiving therapy rather than the number of patients receiving care of adequate quality is not in anyone's interest, not patients', not their families', not the health system's and not society's, a lesson learned decades ago with tuberculosis treatment.

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References

1. Bautista S, Mane A, Bertozzi SM. **Economic impact of antiretroviral therapy prescription decisions in the context of rapid scaling-up of access to treatment: lessons from Mexico.** *AIDS* 2006; **20**:101-109.
2. Stover J, Bertozzi S, Gutierrez JP, Walker N, Stanecki KA, Greener R, *et al.* **The global impact and net costs of scaling-up prevention programs for HIV/AIDS in low- and middle-income countries through.** *Science* 2006; **311**:1474-1476.
3. Gutiérrez JP, Johns B, Adam T, Bertozzi SM, Edejer TT, Greener R, *et al.* **Achieving the WHO/UNAIDS antiretroviral treatment 3 by 5 goal: what will it cost?** *Lancet* 2004; **364**:63-64.

HIV-infected patients with isolated anti-HBc antibodies, the detection of HBV DNA ranges from zero to 36.6% [4-6]. The discrepancies among studies are mainly the result of the methods used to quantify HBV replication, and the use of antiretroviral therapy, especially lamivudine and tenofovir, both of which have anti-HBV activity. In these patients, HBV reactivation may be induced by HAART, by the emergence of lamivudine-resistant HBV,

or by lamivudine withdrawal [7]. We report a case of HBV reactivation with severe hepatitis flare-up in an HIV/HCV-co-infected patient with isolated anti-HBc antibodies during combination therapy with peginterferon alpha-2a and ribavirin.

The patient was a 40-year-old woman diagnosed with HIV/HCV co-infection in 1988. She had isolated anti-HBc antibodies and had been polymerase chain reaction-negative for HBV DNA since 2003 (HBV 3.0 assay; Bayer Diagnostics, Tarrytown, New York, USA, detection limit 3.3 log copies/ml). She had had no antiretroviral therapy since 2003. She weighed 40 kg. She was infected by HCV genotype 3a and her HCV-RNA level was 7.55 log copies/ml (HCV RNA 3.0 assay; Bayer Diagnostics, detection limit 3.5 log copies/ml). Liver enzyme activities were normal. The CD4 cell count and the HIV-RNA level were 412 cells/ μ l and 25 215 copies/ml, respectively. In September 2005, therapy with peginterferon alpha-2a 135 μ g/week and ribavirin 600 mg/day was started. HCV RNA became undetectable by quantitative polymerase chain reaction at week 12. In the fourth month of therapy she became fatigued and jaundiced. The alanine aminotransferase level was 2991 U/l (normal < 60 U/l) and the total bilirubin level was 343 μ mol/l (normal < 17 μ mol/l). Immunoglobulin M antibodies to hepatitis A virus and antibodies to hepatitis delta virus were negative. HCV RNA was negative (Versant HCV RNA; Bayer Diagnostics, qualitative lower detection < 10 IU/ml). HBV DNA became detectable (> 8.0 log copies/ml) for the first time. Hepatitis B surface antigen and hepatitis B e antigen became positive. Anti-HBc IgM was negative. Peginterferon alpha 2a and ribavirin were replaced by lamivudine and adefovir, which was followed by a gradual normalization of liver function tests. After 4 months HBV DNA became undetectable. Hepatitis B surface antigen and hepatitis B e antigen also became negative. HCV viraemia remained negative 6 months after the end of peginterferon and ribavirin therapy.

Interferon therapy is indicated in the treatment of both HCV and HBV infection. The reactivation of HBV infection during interferon therapy is rare, and exemplifies the complexity of viral dominance in patients infected with multiple hepatitis virus [8,9]. HCV can interfere with HBV infection, with a decrease in the replication of both viruses but especially that of HBV [3,8]. HBV reactivation after a decrease in HCV replication in this patient with isolated anti-HBc

antibodies during interferon therapy suggests that interferon therapy may have undermined the suppressive effect of HCV on HBV replication.

In conclusion, HBV reactivation may occur during peginterferon-ribavirin combination therapy in HIV/HCV-co-infected patients with isolated anti-HBc antibodies, even when HBV DNA in undetectable before the initiation of HCV therapy, suggesting that careful monitoring is necessary.

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References

1. Larsen C, Pialoux G, Salmon D, Antona D, Piroth L, Le Strat Y, et al. **Prevalence of hepatitis B and C virus co-infections in the HIV-positive population, France June 2004 [in French].** *Bull Epidémiol Hebd* 2005; **23**:109–112.
2. Cacciola I, Pollicino T, Squadrito G, Cerenzia G, Orlando ME, Raimondo G. **Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease.** *N Engl J Med* 1999; **341**:22–26.
3. Brechot C, Thiers V, Kremsdorf D, Nalpas B, Pol S, Paterlini-Brechot P. **Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen: clinically significant or purely "occult"?** *Hepatology* 2001; **34**:194–203.
4. Neau D, Winnock M, Jouvencel AC, Faure M, Castera L, Legrand E, et al. **Occult hepatitis B virus infection in HIV-infected patients with isolated antibodies to hepatitis B core antigen: Aquitaine cohort, 2002–2003.** *Clin Infect Dis* 2005; **40**:750–753.
5. Wagner AA, Denis F, Weinbreck P, Loustand V, Autofage F, Rogez S, Alain S. **Serological pattern 'anti-hepatitis B core alone' in HIV or hepatitis C virus-infected patients is not fully explained by hepatitis B surface antigen mutants.** *AIDS* 2004; **18**:569–571.
6. Nunez M, Rios P, Perez-Olmeda M, Soriano V. **Lack of 'occult' hepatitis B virus infection in HIV-infected patients.** *AIDS* 2002; **16**:2099–2101.
7. Bani-Sadr F, Maillard A, Ponscarne D, Scieux C, Molina JM. **Reactivation of HBV replication in HIV-HBV infected patients.** *Am J Med* 2003; **114**:768–769.
8. Villa E, Grottola A, Trande P, Seium Y, Rebecchi AM, Dugani A, Mananti F. **Reactivation of hepatitis B virus infection induced by interferon (IFN) in HBsAg-positive, antiHCV-positive patients.** *Lancet* 1993; **341**:1413.
9. Yalcin K, Degertekin H, Yildiz F, Kilinc N. **A severe hepatitis flare in an HBV-HCV coinfecting patient during combination therapy with alpha-interferon and ribavirin.** *J Gastroenterol* 2003; **38**:796–800.