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Response to 'Does immune reconstitution promote active tuberculosis in patients receiving highly active antiretroviral therapy?' *AIDS*, 22 July 2005

We agree with Breen *et al*. [1] that the start of antiretroviral therapy (ART) in Africa and other tuberculosis endemic regions is likely to unmask large numbers of cases of undiagnosed active tuberculosis. It is very important that healthcare providers in these settings are aware of this phenomenon and understand the issues involved in management.

In a recent retrospective notes review of 131 consecutive patients treated for tuberculosis at our clinic in Kampala, 29 (22%) were patients not known to have tuberculosis, who presented within weeks of starting ART (median of 8 weeks).

A good example of such a case is that of a 32-year-old man who had become increasingly unwell over a long period, with weight loss, low-grade fevers and an intermittent cough. Examination revealed a wasted patient, oral candidiasis but no specific features suggestive of active tuberculosis such as chest signs or significant lymphadenopathy. No temperature above 37 °C was recorded at any of his numerous clinic visits. Investigations included a normal chest radiograph (see Fig. 1a), three negative sputum tests for acid fast bacilli and a CD4 cell count of 75 cells/μl. It was decided that there was not enough evidence for active tuberculosis and it that it was necessary to start ART without further delay. Thirteen days after starting the generic combination of nevirapine, stavudine and lamivudine the patient presented to our clinic acutely unwell with high-grade fever and a persistent dry cough. Examination revealed a temperature of 40 °C but no localizing signs. A chest radiograph (see Fig. 1b) revealed obvious milary infiltrations involving all lung zones. A blood slide for malaria and routine blood cultures were negative. The patient was started on standard quadruple antituberculous therapy (ATT), and was switched from his nevirapine-based regimen to efavirenz, zidovudine and lamivudine. He was also started on a course of prednisolone at a dose of 30 mg for 7 days. After one month he had improved significantly with no more fevers or respiratory symptoms. His appetite had improved and he had started to gain weight.

It should be clear that providers in tuberculosis endemic regions need to try to exclude active tuberculosis before starting ART in HIV-infected patients. Their ability to do

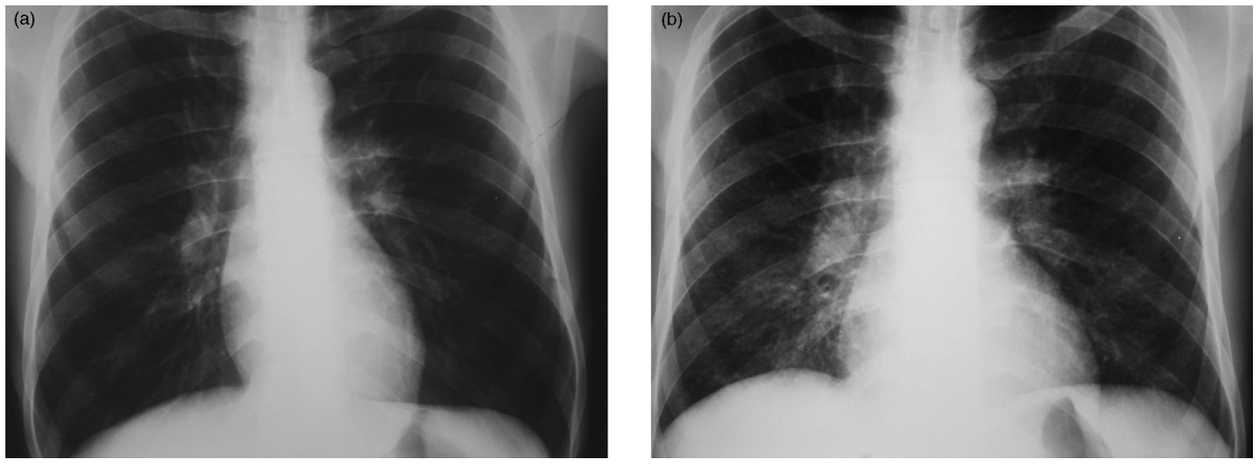

Fig. 1. Chest radiograph at baseline (a) and after 13 days of antiretroviral therapy (b).

this is, however, limited by the diagnostic capabilities of most clinics in these settings. Facilities for the safe induction of sputum, bronchoscopy and any tuberculosis culture are seldom available. We believe that providers should not therefore delay the start of ART in severely immunosuppressed patients because they are worried about the possibility of tuberculosis, but are not confident in making this diagnosis and therefore starting ATT. Doing so would risk further deterioration of the patient and the occurrence of other severe opportunistic infections. Starting ART might be considered a diagnostic test for occult disease. If there is active tuberculosis then it may well present within a few weeks. Providers should therefore watch such patients closely after starting ART. Incidence studies have shown that the median time of immune reconstitution inflammatory syndrome (IRIS) against known tuberculosis may be as early as 12 days [2]. It is our experience that patients may present with unmasked tuberculosis as early as 7 days.

If tuberculosis does present, how should these patients be managed? Tuberculosis must be treated with the standard quadruple regimen. Unless the IRIS is life threatening, ART should be continued. Providers must therefore be aware of the interaction between nevirapine and rifampicin, and should therefore switch to an efavirenz-based regimen if possible [3]. If not, then the patient's ART may need to be stopped. Providers should be aware that non-nucleoside drugs have a long half-life and need to be 'lead out' by continuing the nucleoside analogue backbone for a further week [4].

The role of steroids in IRIS events does not have a large evidence base [5]. It is our experience, however, that this is a safe and effective means of treating through such inflammatory episodes. Care must be taken in counseling these patients (who are often managed as outpatients) about what drugs they are taking and how to take them. The pill burden of ART, ATT and steroids can be quite confusing for the unwell patient who may well opt to just take a proportion of what they have been prescribed unless the situation has been adequately explained.

Despite these challenges, such unmasking episodes can be managed successfully in resource-limited settings. Breen *et al.* [1] should be commended in highlighting this important clinical challenge.

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Cryptococcocal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme

We read with interest the recent paper by Lortholary *et al.* [1] describing cryptococcocal immune reconstitution disease (IRD) in France. This is an increasingly recognized complication of the initial weeks of antiretroviral treatment (ART) [1–5]. However, to our knowledge, the frequency of cryptococcocal IRD in low-income countries has not previously been reported.

We run a community-based ART programme in Gugulethu, Cape Town, South Africa [6]. Between September 2002 and November 2004, 434 treatment-naive patients started triple-drug ART according to WHO 2002 treatment guidelines [7]. The patients' mean age was 34 years, their median blood CD4 cell count was 86 cells/μl [interquartile range (IQR) 46–146 cells/μl], and the median plasma HIV load was 76 337 copies/ml (IQR 32 723–192 772 copies/ml). A total of 137 patients (32%) had WHO stage 4 disease, and among these cryptococcal meningitis was the AIDS-defining illness in 18 (13%). These diagnoses were made a median of 7 months (range 2–24 months) before the initiation of ART. According to national guidelines, cryptococcal meningitis was treated with fluconazole 400 mg/day for 8 weeks followed by 200 mg/day as secondary prophylaxis.

At data censorship in February 2005, the median follow-up was 46 weeks. During a total of 460 person-years of observation (PYO), nine patients developed either