Correspondence

AIDS 2005, **19**:2043–2055

Potential hazard of pharmacokinetic interactions between lopinavir–ritonavir protease inhibitors and irinotecan

The use of concomitant chemotherapy and highly active antiretroviral therapy (HAART) has been demonstrated to be feasible and effective in reducing morbidity associated with opportunistic infections and to improve overall survival in patients with HIV-related malignances [1,2]. However, such combination therapy causes severe toxicity, including neutropenia [3,4]. It has been hypothesized that such unpredictable toxicity can be related to pharmacokinetic interactions.

Here, we report on the effect of a lopinavir–ritonavir (LPV/r) protease inhibitor combination on the pharmacokinetics of irinotecan, in an HIV-infected, 42-year-old man with Kaposi's sarcoma. The patient was enrolled in an ongoing phase II clinical trial, approved by the Institutional Review Board and the Ethics Committee to evaluate the efficacy of HAART and irinotecan therapy in HIV patients with Kaposi's sarcoma.

The HAART regime in this patient consisted of a twice daily oral administration of 400 mg lopinavir and 135 mg ritonavir protease inhibitor combination (kaletra) in combination with a twice daily 300 mg zidovudine and 150 mg lamivudine (combivir) nucleoside reverse transcriptase combination. Chemotherapy consisted of 150 mg/m^2 irinotecan administered by 1.5 h infusion at days 1 and 10, repeated every 3 weeks. Standard ondasentron treatment 30 min before the irinotecan infusion and a 6-day treatment with 300 μg/day granulocyte colony stimulating factor was also administered. Before the chemotherapy course, the patient underwent a 2-month treatment with the above HAART regime.

The pharmacokinetic profile of irinotecan administered alone was investigated on the first day of the first chemotherapy cycle, after a 2-day protease inhibitor wash out, whereas the pharmacokinetics of irinotecan in combination with LPV/r was performed on the first day of the second chemotherapy cycle. The patient on this occasion received 50% of the irinotecan dose (75 mg/m^2) because of persistent grade G2 WHO neutropenia, in agreement with clinical protocols. The plasma concentration of irinotecan, its active metabolite SN38, the inactive SN38 glucoronide and the 7-ethyl-10[4-N-(5 aminopentanoic acid)-1-piperidine]-carbonyloxy-camptothecin (APC) oxidized metabolite were determined over a 50-h time interval by using a validated high-pressure liquid chromatography method [5].

Irinotecan is a prodrug metabolized *in vivo* to form the active metabolite SN38, which is further eliminated as a glucoronide metabolite [6]. Furthermore, irinotecan undergoes significant oxidative metabolism by the same P450 isoenzyme CYP3A4 involved in the metabolic clearance of both lopinavir and ritonavir protease inhibitors, prevalently to form the inactive APC metabolite [6,7]. Therefore, interferences at the level of this common metabolic pathway could occur.

In the case study reported here, we found that the co-administration of LPV/r protease inhibitors resulted in a marked inhibition of the APC production from CPT11. The area under the curve $(AUC)^{APC} : AUC^{Irinotecan}$ metabolic ratio was 20-fold lower during the course of irinotecan plus LPV/r (Table 1). This was in agreement with the 10-fold reduction of APC AUC_∞ normalized for dose (AUC_∞/dose) during the co-administration of irinotecan with LPV/r compared with that observed when irinotecan was administered alone. The reduced production of APC metabolite was associated with a 34% reduction of the irinotecan total body clearance and a twofold increase of the AUC_∞/dose of the active metabolite SN38. This suggests that the inhibition of CYP3A4 activity by LPV/r may drive the irinotecan metabolism to an activation pathway. The relative extent of irinotecan to SN38 conversion expressed as $AUC^{SN38} : AUC^{Irinotecan}$ was 1.5-fold greater during LPV/r combination therapy compared with irinotecan alone. These results are in agreement with a previous study by Kehrer *et al.* [8], which reported that ketoconazole, used as model inhibitor of CYP3A4, determined an almost complete inhibition of APC production associated with a shunt of irinotecan metabolism to SN38. Although in our study the patient received 50% of the irinotecan dose, during the course of irinotecan plus LPV/r, he was subjected to approximately the same SN38 AUC reported when the 100% irinotecan dose was administered alone. A persistent grade G2 WHO neutropenia, still observed during the second cycle of irinotecan plus LPV/r, probably as a result of the relatively high SN38 plasma levels, forced the patient to abandon the clinical protocol.

These results suggest that to avoid hazard and potential severe toxicity, caution should be taken when an LPV/r protease inhibitor combination is co-administered with irinotecan. Clinicians who intend using irinotecan-based chemotherapy in combination with HAART regimes containing LPV/r should carefully monitor their patients

Table 1. Effect of lopinavir–ritonavir protease inhibitor combination on pharmacokinetics of irinotecan.

	Irinotecan	Irinotecan + LPV/r	Percentage differences (%)[a]
Irinotecan			
Dose (mg m^{-2})	150	75	−50
AUC_∞/dose ($\mu g\ l^{-1}\ h\ mg^{-1}$)	22.31	33.70	51
Clearance ($l\ h^{-1}\ m^{-2}$)	25.90	17.15	34
APC			
APC AUC_∞/dose ($\mu g\ l^{-1}\ h\ mg^{-1}$)	2.31	0.16	−93
AUC^{APC} : $AUC^{Irinotecan}$	0.10	0.005	−95
SN38			
AUC_∞/dose ($\mu g\ l^{-1}\ h\ mg^{-1}$)	0.53	1.17	121
AUC^{SN38} : $AUC^{Irinotecan}$	0.024	0.035	46
SN38G			
AUC_∞/dose ($\mu g\ l^{-1}\ h\ mg^{-1}$)	1.76	3.45	96
AUC^{SN38G} : $AUC^{Irinotecan}$	0.079	0.102	29

APC, 7-Ethyl-10[4-N-(5 aminopentanoic acid)-1-piperidine]-carbonyloxycamptothecin; AUC, area under the curve; LPV/r, lopinavir/ritonavir.
[a]Percentage of difference referred to the pharmacokinetics of irinotecan administered alone.

for potential adverse effects, and irinotecan dose reduction should be considered to avoid severe toxicity. Further pharmacokinetic–pharmacodynamic investigations, involving a large number of homogeneously treated patients, will provide a definite indication on irinotecan dose adjustments in patients receiving irinotecan in combination with LPV/r protease inhibitors.

Giuseppe Corona[a], Emanuela Vaccher[b], Giulio Cattarossi[a], Ivana Sartor[b] and Giuseppe Toffoli[a],
[a]Experimental and Clinical Pharmacology Unit, and [b]Division of Medical Oncology A, National Cancer Institute CRO–IRCCS, Aviano (PN), Italy.

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Response to Foss *et al*., 'Care should be taken when promoting microbicide use among sex workers who are able to use condoms consistently'

Mathematical modeling analyses by ourselves [1] and Foss *et al*. [2] predicted that vaginal microbicides could substantially reduce the risk of HIV acquisition. Our analysis purposely considered a high-risk group of women, namely, female sex workers (FSW) in a high-prevalence resource-constrained setting. We determined that increasing microbicide use would have a greater impact on reducing risk than increasing microbicide efficacy. We also quantified the breakeven threshold for the level of condom replacement that could be tolerated, given microbicide efficacy and usage, so that the risk of HIV acquisition would not increase [1]. We predicted that even if the microbicides that become available are low to moderately effective, the probability that risk in FSW would increase (as a result of replacing condoms with microbicides) would be low. Furthermore, in our threshold analysis, we considered the worst-case scenario of complete condom replacement; if only partial condom replacement occurred, results would be more optimistic. Our conclusions assume low-to-moderate condom use before the introduction of microbicides. As stated by Foss *et al*. [3], and as we discussed in our analysis [1], if condom use (very effective protection) is high among all FSW clients, and condoms are replaced by low efficacy microbicides then risk could increase. A primary purpose of our analysis [1] was to emphasize that, as with all prevention methods, replacing one prevention method with another can result in a perverse outcome depending on the relative usages and efficacies [4]. We have shown that microbicide use would be beneficial in reducing the risk of HIV acquisition for the majority of individuals [1].

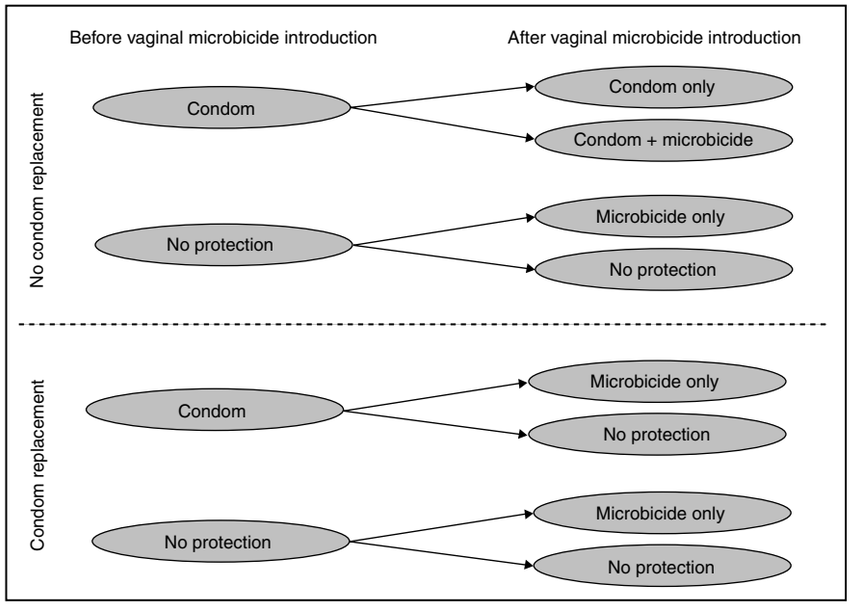

Fig. 1. Schematic diagram of the possible types of protection options available to female sex workers that are included in our model. Before the introduction of vaginal microbicides female sex workers (FSW) have two protection options (using condoms or using no protection). After the introduction of vaginal microbicides, four options are available, but each woman in our model has two options for protection depending on what protection she used before the introduction of microbicides and whether she will completely replace her condom use with microbicides (condom replacement) or not (no condom replacement).

Despite some differences in the mathematical framework, our basic conclusions agree with those of Foss *et al.* [2]. We used risk equations to estimate the individual risk of HIV acquisition given microbicide use [1], and concluded, as did Foss *et al.* [2], that condom replacement will not be a significant concern in populations in which condom use is low. However, our risk equations [1] emphasized the different types of protection used pre and post-microbicides (Fig. 1), whereas Foss *et al.* [2] emphasized transmission heterogeneity due to sexually transmitted diseases and high viremia. Individuals may have sex using: (i) no protection; (ii) condoms only; (iii) microbicides only; or (iv) both condoms and microbicides. Foss *et al.* [2] did not consider protection with both condoms and microbicides, we did [1]. We modeled heterogeneity and uncertainty in our parameters, by performing uncertainty and sensitivity analyses using large ranges for all parameters [1]. In contrast, Foss *et al.* [2] only used single point estimates of parameters. Foss *et al.* [2] considered only microbicides of 50% effectiveness, whereas we analysed low-to-moderate efficacy (30–50%) and moderate-to-high efficacy (50–80%) microbicides [1]. We assumed that condom use is low (10–50%), because even when HIV is widespread many individuals do not consistently use condoms [5].

Although some small groups of FSW (in Asia, for example) have reported consistently high condom use with their clients, this level of protection is unusual, particularly in sub-Saharan Africa [6,7]. Much of the HIV/AIDS pandemic has spread through heterosexual intercourse, indicating that, consistent with large-scale sexual behavior survey data [7,8], unprotected risky sexual behavior can be common among heterosexual partners. Current condom usage is generally much less than the level that would yield a perverse outcome if condoms were abandoned altogether in favor of reasonably efficacious microbicides. This is especially true in the developing world, where only approximately 1% of sexually active women reported condom use in the past month [7]. The average change in risk will vary between individuals; however, as condom usage is generally low, we have shown that even using partly effective microbicides would decrease the risk for most individuals [1]. There will always be exceptions in which individuals replace high condom use with microbicides, and increase their risk. However, an increase in the individual risk for some should be considered in the context of overall population-level incidence. The proportion of individuals for whom risk would increase is the important factor. As this proportion is small, the population-level incidence would not increase. We recommend that microbicide development should not be hindered by concerns that some small groups may increase their risk, especially if the majority of individuals using microbicides would lower their individual risk, resulting in decreased population-level incidence.

There is much excitement surrounding the potential of vaginal microbicides as a female-controlled prevention method to stem HIV/AIDS transmission. Although there is no need to be pessimistic about introducing microbicides, the promotion of continued condom use and other forms of protection should be maintained and coupled with educational campaigns. Clearly, as the HIV/AIDS pandemic rages on, there is a great need for additional/alternative forms of protection such as microbicides.

David P. Wilson[a], Erin N. Bodine[a], Robert J. Smith[a,b] and Sally M. Blower[a], *[a]Department of Biomathematics and UCLA AIDS Institute, School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA; and [b]Department of Mathematics and College of Veterinary Medicine, The University of Illinois at Urbana–Champaign, Urbana, IL, USA.*

The first two authors contributed equally to the formulation of this response letter.

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Zidovudine-induced pure red cell aplasia presenting after 4 years of therapy

Reversible pure red cell aplasia is a recognized complication of both zidovudine and lamivudine, typically occurring within the first 3 months of therapy [1,2]. We report the case of a 29-year-old man with HIV, severe haemophilia A and hepatitis C, who developed reversible pure red cell aplasia 4 years after commencing zidovudine.

The patient presented to our centre in September 2004 with a 2-week history of exertional dyspnoea and palpitations. He had severe haemophilia A and chronic hepatitis C (genotype 3B), which had never been treated. HIV was diagnosed in 1984; highly active antiretroviral therapy (HAART) was commenced in February 1999 with zidovudine, lamivudine and indinavir. In 2002, his HAART regimen was changed to Trizivir (zidovudine, abacavir and lamivudine).

As he had previously developed Stevens–Johnson syndrome on co-trimoxazole, monthly nebulized pentamidine was used as *Pneumocystis carinii* prophylaxis. His haemophilia A was managed with plasma-derived factor VIII on demand (Fandhi 3000 units), which he used two to three times a month. He was taking no other medications.

On examination, he appeared pale but otherwise well. There was conjunctival pallor, but no jaundice. Respiratory and abdominal examination was normal. He had a hyperdynamic circulation with a grade 3/6 ejection systolic flow murmur confined to the left sternal edge. There were no symptoms or signs of bleeding.

Initial laboratory investigations showed a severe macrocytic anaemia with a haemoglobin level of 3.5 g/dl and mean corpuscular volume of 115 fl. The reticulocyte count was low at 3×10^9/l. Platelet and white cell counts were normal. The blood film showed an oval macrocytosis. On review of previous blood counts, the patient had had a macrocytosis (range 117–122 fl) without anaemia since commencing HAART in 1999.

At the time of presentation, his HIV-RNA level was less than 50 copies/ml and the CD4 cell count was 391 cells/μl. Serum ferritin, B12 and folate were normal, as were plasma methylmalonic acid and homocysteine (functional markers of B12 and folate deficiency, respectively). Renal and liver function tests were normal. The serum erythropoietin level was appropriately raised at 584 U/l.

Bone marrow aspirate and trephine biopsy were performed with factor VIII cover. The aspirate showed a megaloblastic picture with maturation arrest of the erythroid series at the early erythroblast stage. The trephine biopsy was hypercellular and megaloblastic with disorganized haematopoeisis.

Parvovirus IgG was positive but IgM was negative. Mycoplasma serology was negative. Bone marrow trephine stains for acid-fast bacilli, fungi, parvovirus, human herpes virus 8 and Epstein–Barr virus were negative. Polymerase chain reaction testing of bone marrow aspirate for parvovirus B19 and HHV-6 DNA

was negative. Peripheral blood flow cytometry for paroxysmal nocturnal haemoglobinuria was negative.

Four units of packed red cells were transfused, and the patient was monitored for 10 days. As he failed to mount a reticulocyte response and the virology findings proved negative, his HAART regimen was changed to lamivudine, tenofovir and efavirenz. Eight days after stopping zidovudine, he mounted a reticulocyte response of 120×10^9/l. The full blood count normalized 20 days after the cessation of zidovudine. Six months later, he remains well with a normal full blood count and normal mean corpuscular volume.

Pure red cell aplasia is a well-documented adverse reaction of HAART regimens containing both zidovudine and lamivudine. In this instance, the discontinuation of zidovudine, but not of lamivudine, led to the prompt resolution of the anaemia. This is the first published case of zidovudine-induced pure red cell aplasia occurring so late in zidovudine therapy, and illustrates that this complication is not restricted to the first 3 months of treatment.

Robert Weinkove, Savita Rangarajan, Jon van der Walt and Ranjababu Kulasegaram, *St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK.*

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Pulmonary *Mycobacterium celatum* immune restoration disease: immunopathology and response to corticosteroid therapy

Antiretroviral therapy (ART) in immunodeficient HIV patients may be complicated by mycobacterial immune restoration disease (IRD) resulting from an immunopathological response to subclinical infections by non-tuberculous mycobacteria (NTM) [1]. The most common presentation is lymphadenitis associated with *Mycobacterium avium* complex infection. Pathogenic mechanisms in mycobacterial IRD are incompletely understood, but data accumulated thus far suggest that delayed-type hypersensitivity (DTH) responses to mycobacterial antigens are a cause of tissue inflammation [1–3]. We report a case of *Mycobacterium celatum* IRD, presenting with pneumonitis, and present data illustrating the immunopathological nature of this disease.

A 48-year-old man with past *Pneumocystis jiroveci* pneumonia and disseminated cytomegalovirus infection was commenced on lopinavir/ritonavir, zidovudine and lamivudine when the CD4 T-cell count was 48 cells/μl (6%) and the plasma HIV-1-RNA level was greater than 100 000 copies/ml. He was receiving prophylactic azithromycin and maintenance valganciclovir. On day 11 of ART he developed fever, and chest radiography (previously normal) showed patchy consolidation in both lungs. A computed tomography (CT) scan of the thorax demonstrated an area of consolidation in the left upper lobe and scattered nodular opacities in the left lower lobe and right lung (Fig. 1a). Sputum collected on days 12, 13 and 14 of ART yielded *M. celatum* from both mycobacteria growth indicator tube media and Löwenstein–Jensen agar, confirmed by 16S ribosomal RNA gene sequencing. However, repeated culture of blood using the BACTEC 460 system did not demonstrate mycobacteremia.

On day 27, the plasma HIV-1-RNA level had decreased to 933 copies/ml and the CD4 T-cell count had increased to 144 cells/μl (24%). DTH skin testing demonstrated an 18 mm response to tuberculin and a 10 mm response to *Mycobacterium avium* purified protein derivative (PPD) using antigens from the Commonwealth Serum Laboratories (Melbourne, Australia). Skin testing had not been performed before commencing ART, but anergy was likely given the severity of his immunodeficiency [4]. A punch skin biopsy was taken from the tuberculin skin test site and immunohistological examination, using murine monoclonal antibodies to CD3, CD4 and CD8 (Nova Castra, Newcastle-upon-Tyne, UK), demonstrated a lymphocytic infiltrate, which consisted predominantly of T cells with a CD4/CD8 T-cell ratio of 8 : 1.

Whole blood samples were tested for mycobacteria-specific T cells using IFN-γ release assays (QuantiFERON-TB or QuantiFERON-TB Gold; Cellestis, Carnegie, Victoria, Australia) according to the manufacturer's instructions [5,6]. Specific activities of 64% (reference $< 15\%$) and 46% (reference $< 20\%$) were obtained with tuberculin and *M. avium* PPD, respectively, using the QuantiFERON-TB assay, but there was no response to the ESAT-6 or CFP-10 antigens of tuberculin using the QuantiFERON-TB Gold assay. These findings suggest the presence of T cells reacting with antigens of NTM. Five years previously, when his CD4 T-cell count was 1218 cells/μl, the QuantiFERON-TB assay did not show specific activity to either tuberculin or *M. avium* PPD.

Pentoxifylline, a tumour necrosis factor inhibitor, was commenced in an attempt to suppress inflammation, but

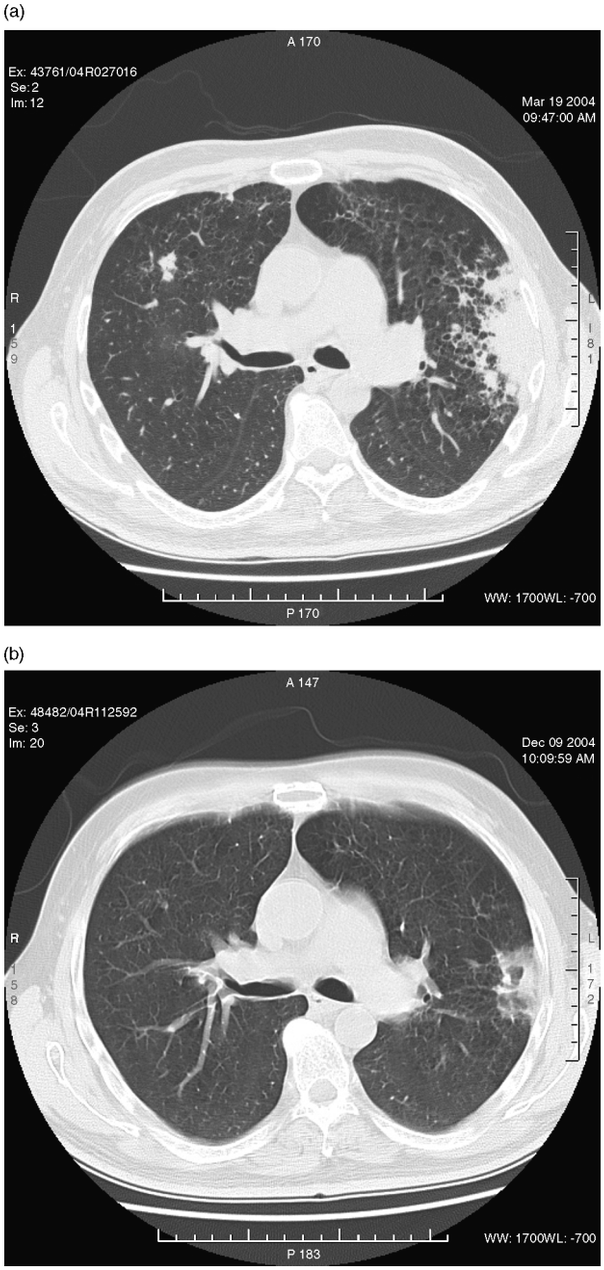

Fig. 1. High resolution computed tomography scan of the thorax at presentation with *Mycobacterium celatum* immune restoration disease (a) and 24 weeks after commencing prednisone (b). At presentation the scan demonstrates an area of consolidation in the left lung and a nodule in the right lung consistent with granulomatous inflammation. Residual cystic changes from previous *Pneumocystis jiroveci* pneumonia are also present.

was ceased after 4 weeks because it was ineffective. Anaemia and leukopenia had been present since starting ART and were not improved by the cessation of valganciclovir or the substitution of tenofovir for zidovudine. The serum C-reactive protein level, which had declined after treatment of *P. jiroveci* pneumonia and cytomegalovirus infection, rose after the commencement of ART. Prednisone 10 mg a day was initiated and was associated with a resolution of the cytopenias and normalization of serum C-reactive protein levels. The patient's symptoms resolved completely and a CT scan undertaken 24 weeks after commencing prednisone showed significant improvement (Fig. 1b).

This is the first report of *M. celatum* IRD. Previous reports of *M. celatum* disease in HIV-1 patients have not presented data on the onset of disease relative to the commencement of ART. It is possible that some of these cases were IRD [7–9].

This case provides valuable information about the pathogenesis of IRD. Pulmonary inflammation, which on CT scanning was reported to be consistent with granulomatous inflammation, was associated with the repeated isolation of *M. celatum* from sputum and a cutaneous DTH response to tuberculin. Histopathological examination of the DTH reaction showed a tissue predominance of CD4 T cells, suggesting that the immune response was mediated by tuberculin-specific CD4 T cells. However, whole blood IFN-γ release assays demonstrated the presence of blood T cells responding to NTM antigens, presumably reflecting the presence of *M. celatum*-specific CD4 T cells crossreacting with antigens within tuberculin.

The pulmonary inflammation was associated with persistent anaemia and leukopenia and increased inflammatory markers. Apart from prophylactic azithromycin, specific antimycobacterial therapy was not given to treat the pneumonitis. Corticosteroid therapy resulted in the resolution of the cytopenias and pulmonary lesions associated with the normalization of inflammatory markers. These findings highlight the importance of immunopathological responses to mycobacterial antigens and the efficacy of anti-inflammatory therapy in mycobacterial IRD.

Helen C. Bell[a], Christopher H. Heath[b,c] and Martyn A. French[a,d], *Departments of [a]Clinical Immunology and Biochemical Genetics, [b]Microbiology and Infectious Diseases, Royal Perth Hospital, Perth, Western Australia, Schools of [c]Medicine and Pharmacology, and [d]Pathology and Surgery, University of Western Australia, Perth, Western Australia.*

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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

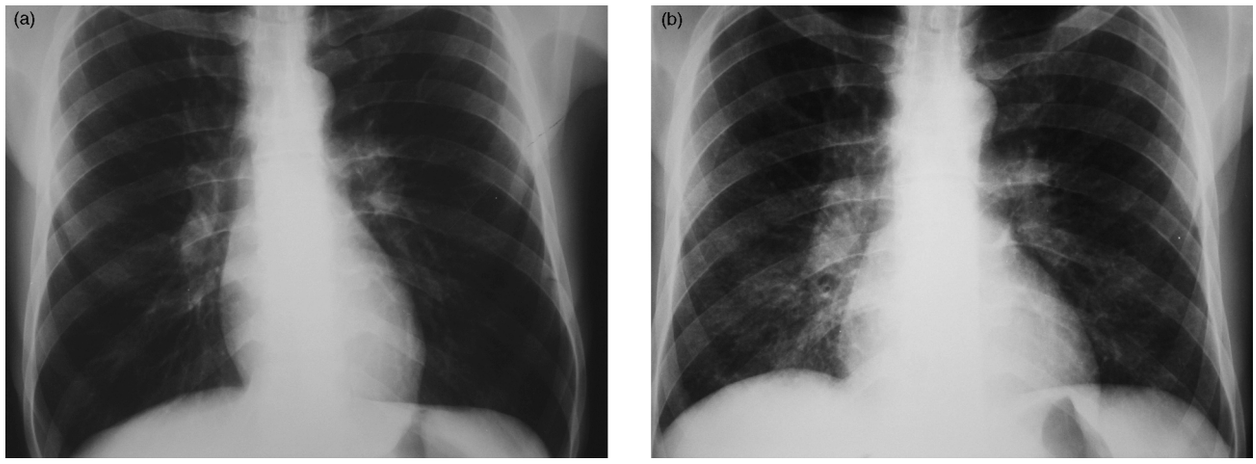

Fig. 1. Chest radiograph at baseline (a) and after 13 days of antiretroviral therapy (b).

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.

Laurence John[a], Joshua Baalwa[a], Pearl Kalimugogo[a], Evelyn Nabankema[a], Barbara Castelnuovo[a], George Muhindo[b], Robert Colebunders[a,c,d] and Andrew Kambugu[a], *[a]Infectious Disease Institute, Mulago, Kampala, Uganda; [b]Mbarara University of Science and Technology, Mbarara, Uganda; [c]University of Antwerp, Antwerp, Belgium; and [d]Institute of Tropical Medicine, Antwerp, Belgium.*

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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

Table 1. Features of nine cases of central nervous system cryptococcosis during the initial weeks of antiretroviral treatment.

	Age	Sex	Previous CM (months pre-ART)	Nadir CD4 (cells/μl)	Viral load (log copies/ml)	Weeks ART	Clinical presentation	CSF analysis							Outcome
								P	L	Protein (g/l)	Glucose (mmol/l)	India ink	Ag test	Culture	
1.	36	M	No	9	4.85	1	Meningitis	0	3	0.58	1.4	pos	nd	pos	Died
2.	40	F	Yes (7)	23	5.53	4	Meningitis	4	16	8.21	0.3	neg	pos	neg	Died
3.	57	F	Yes (18)	57	5.70	8	Meningitis	94	121	6.4	0.3	nd	pos	neg	Died
4.	33	M	Yes (23)	22	5.70	1	Meningitis	236	137	5.6	0.3	neg	pos	neg	Died
5.	45	F	Yes (2)	54	4.65	1	Paraparesis	0	3	0.52	2.9	pos	pos	neg	Died
6.	51	M	No	24	4.23	4	Meningitis	0	6	0.65	2.7	pos	pos	pos	Survived
7.	35	F	Yes (6)	58	5.64	7	Meningitis	4	44	1.17	2.3	neg	pos	neg	Survived
8.	32	F	No	58	5.58	23	Meningitis	0	34	0.67	2.8	neg	pos	neg	Survived
9.	38	F	Yes (26)	73	4.99	1	Meningitis	206	130	2.59	0.8	nd	pos	neg	Died

ART, Antiretroviral therapy; CM, cryptococcal meningitis; CSF, cerebrospinal fluid analysis: P, polymorphonuclear cells/μl; L, lymphocytes/μl; Ag test, cryptococcal latex agglutination antigen test; nd, not done.

recurrent ($n = 6$) or new ($n = 3$) symptomatic cryptococcal disease of the central nervous system (Table 1). The median duration of ART at the onset of symptoms was 4 weeks. In the first, second and third months of ART, disease incidence based upon the time of symptom onset was 18.2 cases/100 PYO [95% confidence interval (CI) 8.2–40.6], 6.2 cases/100 PYO (95% CI 1.6–25.1) and 0 cases/100 PYO, respectively. Only one case of cryptococcal disease occurred after 12 weeks' ART. Six of the nine patients (66%) died and cryptococcal disease accounted for six out of 22 total deaths (27%) during the first 3 months of ART.

IRD results from the rapid restoration of immune function, leading to an exacerbation of partly treated opportunistic infections or unmasking of previously undiagnosed subclinical infections [8]. Several factors have suggested that IRD was the likely mechanism underlying the presentation of most or all of these cases of cryptococcosis: the very high incidence density rate within the initial weeks of ART, the sudden onset, the typically rapid evolution and fulminant clinical course. Of those with a previous history of cryptococcosis, one-third developed probable IRD. Although this proportion is comparable with other series [2,5], the mortality rate in our series is higher and represents a substantial problem that needs to be addressed to reduce the early mortality during ART among patients in resource-limited settings.

Live organisms, dead organisms or their shed antigens may trigger IRD [8]. Among cases from whom viable organisms are cultured, symptoms may either be caused by IRD or simply represent new opportunistic disease. IRD case definitions that exclude clinically suspected cases with positive cultures increase the specificity of IRD diagnoses but may limit sensitivity. Of the nine patients described, seven had sterile cultures; although cultures from the remaining two cases were positive, a review of their clinical presentation suggested that IRD was potentially the underlying mechanism.

Cryptococcocal IRD is likely to be increasingly frequently encountered in ART programmes in sub-Saharan Africa for several reasons. First, ART programmes in the region are currently inundated with large numbers of patients with very advanced immunodeficiency; such patients are at the greatest risk of developing IRD. Second, HIV-associated cryptococcal disease is common in the region. Third, the local standard of care for cryptococcal meningitis is treatment with oral fluconazole, which is supplied free of charge by the manufacturer. Fluconazole is a fungistatic drug, which is broadly effective as secondary prophylaxis, but has far less efficacy than amphotericin in clearing the organism during the initial treatment phase [9]. We suggest that the use of this agent for primary treatment may increase the risk of cryptococcal antigen persistence within the cerebrospinal fluid (CSF), possibly increasing the risk of IRD during ART.

Among those with a previous history of cryptococcosis, an analysis of CSF before the initiation of ART might be used to identify those with a persistent antigen burden who might then be retreated to reduce the fungal burden before starting ART. However, this strategy may be impractical in view of the huge logistic challenges facing many ART programmes in low-income countries. However, the optimum interval between the treatment of cryptococcal meningitis and the initiation of ART needs to be defined, and clinicians should be made aware of cryptococcal IRD to promote early diagnosis and prompt treatment. Optimal management strategies for cryptococcal IRD need to be defined by future studies, including the choice of antifungal agents, the use of corticosteroids, and the role of the discontinuation of ART.

Stephen D. Lawn[a,c], Linda-Gail Bekker[a], Landon Myer[a,b], Catherine Orrell[a] and Robin Wood[a], *[a]The Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, and [b]Infectious Diseases Epidemiology Unit, School of Public Health*

and Family Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; and [c]Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK.

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Spinal epidural lipomatosis: a manifestation of HAART-associated lipodystrophy

Myelopathy in HIV-infected patients may result from a variety of causes, including HIV-associated vacuolar myelopathy, cytomegalovirus myelitis and spinal cord compression secondary to non-Hodgkin's lymphoma [1]. This report presents a patient with myelopathy secondary to HAART-associated lipodystrophy and spinal epidural lipomatosis (SEL). HAART-associated SEL should be considered as a differential diagnosis in HIV-infected patients presenting with myelopathy.

A 43-year-old homosexual man (CDC stage C3) presented in June 2003 with bilateral leg weakness, unsteady gait and mild urinary retention, which had developed slowly during the previous 12 months. During the previous 2 years, he had developed mild lipodystrophy manifestations with visceral fat accumulation and buccal fat loss. His body status was otherwise unremarkable, with a normal body weight [weight 81 kg, height 186 cm, body mass index (BMI) 23 kg/m^2]. Routine blood tests were also unremarkable. The CD4 cell count was 427 cells/μl and the viral load was less than 50 copies/ml. Non-fasting total cholesterol and triglyceride values were 198 and 283 mg/dl, respectively, while he was on 400 mg bezafibrate per day.

The patient was diagnosed with HIV infection in 1992 when he presented with oral thrush and recurrent anal herpes (CD4 cell count 17 cells/μl). He has received antiretroviral treatment since January 1993, with a total of 10 regimens, including various nucleoside analogue reverse transcriptase inhibitors (didanosine, zidovudine, lamividine, stavudine, and abacavir), non-nucleoside analogue reverse transcriptase inhibitors (delavirdine, viramune), and protease inhibitors (ritonavir, saquinavir, nelfinavir, amprenavir). He experienced virological failure on some of these regimens as a result of non-compliance and the development of resistance. At the time of his presentation in June 2003 the patient was on a HAART regimen (started in March 2000) of 400 mg lopinavir/100 mg ritonavir (Kaletra) plus 300 mg zidovudine/150 mg lamivudine (Combivir) twice a day.

The neurological evaluation in June 2003 revealed myelopathic syndrome, including mild paraparesis, proprioceptive deficits, a positive Romberg's test, decreased vibration sense without gradient, increased muscle tone of the lower extremities, brisk patella tendon and adductor reflexes, and a negative Babinski sign. Lumbar puncture, as well as electromyography and nerve conduction studies, was unremarkable. Sensory evoked potentials from the tibialis nerve revealed a significant bilateral disturbance at the spinal level and established the diagnosis of myelopathy. Magnetic resonance imaging (MRI) documented compression of the spinal cord at the C4–T5 level by extensive epidural lipomatosis (Fig. 1). Other causes of myelopathy, including vitamin B12 and folic acid deficiencies, were excluded [1].

As SEL was considered to be HAART associated, the antiretroviral regimen was switched in July 2003 to a protease inhibitor-sparing regimen consisting of zidovudine/lamivudine/abacavir plus nevirapine. After regimen failure in December 2003 (CD4 cell count 204 cells/μl, viral load 35 300 copies/ml), the medications were switched to a ritonavir-boosted double protease inhibitor regimen consisting of 400 mg lopinavir/100 mg ritonavir

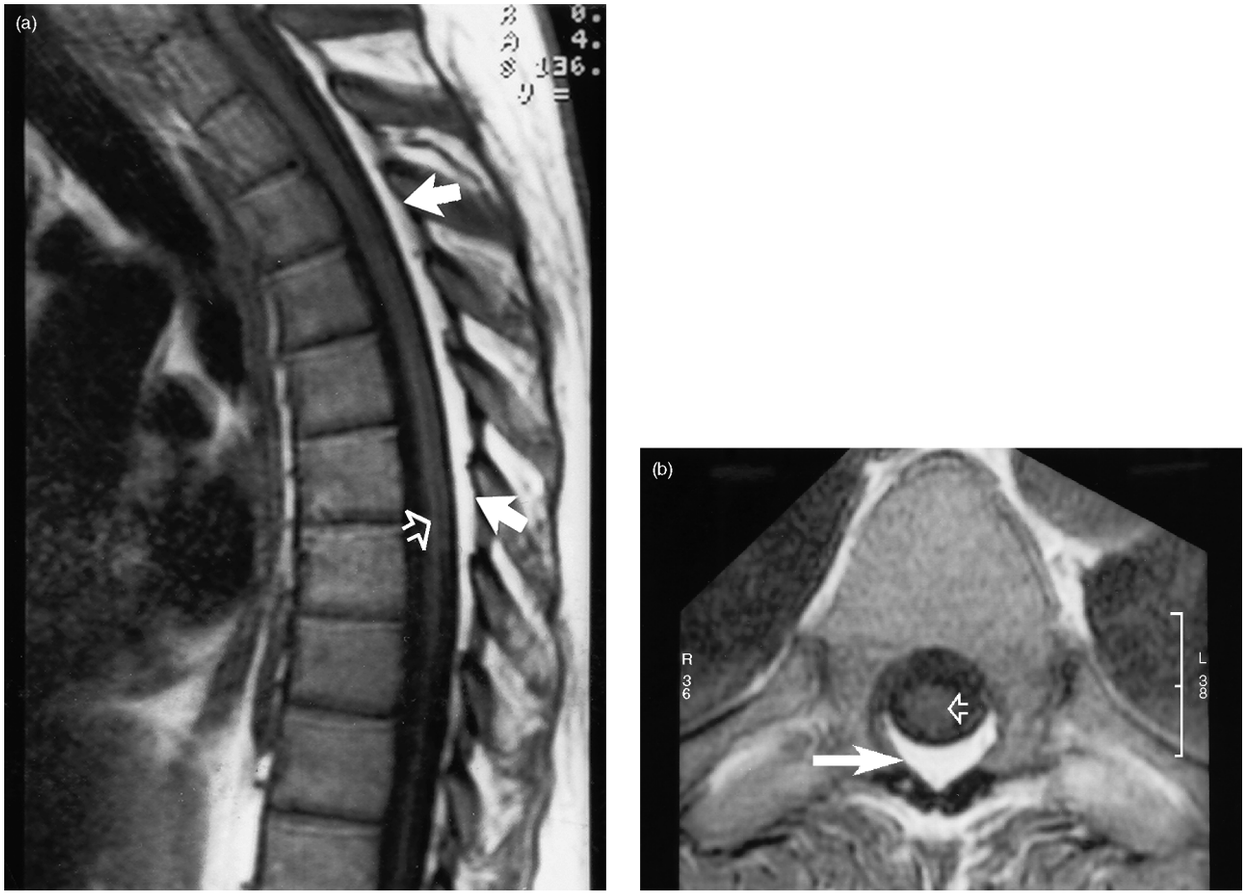

Fig. 1. Magnetic resonance imaging of the spine. (a) Sagittal, T1-weighted view demonstrating an epidural fat pad (white arrow) along the C4–T5 level of the cord (open arrow). (b) Axial, T1-weighted image demonstrating epidural fat (white arrow) at T2–T3, which fills almost one third of the spinal canal and leads to displacement of the cord (open arrow).

(Kaletra) twice a day plus 300 mg atazanavir once a day. After the initial presentation and discontinuation of the Kaletra plus Combivir regimen in July 2003 there were no signs or symptoms of the progression of myelopathy and lipodystrophy. A follow-up evaluation in May 2005 showed findings, including physical status, BMI, neurological examination, sensory evoked potentials and magnetic resonance imaging of the spine, to be stable. Routine blood tests were again unremarkable. The CD4 cell count was 498 cells/μl and the viral load was less than 50 copies/ml. Non-fasting total cholesterol and triglyceride values were 205 and 330 mg/dl, respectively, while he was on 400 mg bezafibrate per day.

SEL is a rather rare condition, with approximately 100 cases discussed in the literature [2]. It is associated with a variety of conditions, including long-term steroid use and endocrinopathies such as Cushing's syndrome or hypothyroidism. Idiopathic SEL occurs almost exclusively in the obese population (BMI > 27.5) and in younger patients (average age 35 years) [3]. We concluded that SEL might be a manifestation of HAART-associated lipodystrophy because our patient revealed typical features of lipodystrophy and other causes of SEL did not apply.

Lipodystrophy manifesting with reduced insulin sensitivity, hyperlipidemia and fat accumulation appears to be primarily caused by the use of protease inhibitors [4,5]. Nucleoside analogue reverse transcriptase inhibitors can also contribute to fat accumulation; although these drugs are primarily associated with subcutaneous fat loss [5]. Fat accumulation usually manifests with visceral fat accumulation, dorsocervical fat pads (buffalo hump) and supraclavicular fat pads [4,5]. Symptomatic HAART-associated SEL appears to be a rare event, and to our knowledge only two cases have been reported so far in the literature. The first patient received long-term steroids together with ritonavir and required subsequent surgical decompression [6]. The second patient received indinavir treatment, with SEL resolving upon the discontinuation of indinavir and continuation of treatment with a protease inhibitor-sparing regimen [7].

Our patient was treated with a variety of protease inhibitors. We speculate that he developed lipodystrophy

and SEL mainly as a result of taking Kaletra. It should be noted that there was no further progression during treatment with Kaletra plus atazanavir over an 18-month follow-up period. Whether the combination of Kaletra with atazanavir, and its favorable metabolic characteristics [8], together with the omission of nucleoside analogues, may have reduced the risk of progression of SEL remains unclear. An alternative explanation might be that fat accumulation is often known to increase for some time and to then remain stable for years thereafter in spite of the continuation of HAART [5].

Dirk Schürmann[a], Jürgen Rademaker[c], Thomas Trottenberg[b], Frank Bergmann[a], Hans Wesselmann[a] and Norbert Suttorp[a], *Departments of [a]Infectious Diseases, and [b]Neurology, Charité, Universitätsmedizin Berlin, Berlin, Germany; and [c]Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA.*

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Atazanavir/ritonavir versus lopinavir/ritonavir: equivalent or different efficacy profiles?

Johnson and colleagues [1] presented results from a randomized clinical trial of atazanavir/ritonavir (ATV/r), lopinavir/ritonavir (LPV/r) and atazanavir/saquinavir in a total of 358 treatment-experienced patients. The conclusion, that ATV/r is as effective as LPV/r, does not seem to be supported by further analysis of the trial data.

The most common primary efficacy analysis of HIV clinical trials is the proportion of patients with HIV RNA under 50 copies/ml, using an intent-to-treat population, in which patients discontinuing randomized medication or with missing data are classified as treatment failures. Clinical trials for drug licensing are normally powered, using this HIV RNA endpoint, to detect differences of at least 10–12% between treatment arms, or to show equivalence or non-inferiority within these limits [2]. A normal regulatory trial powered within these limits would have 250–400 patients per arm. The BMS-045 trial, with approximately 120 patients per arm, is clearly underpowered to assess efficacy by the normal endpoint of HIV RNA 50 copies/ml.

For the BMS-045 trial, the intent-to-treat analysis of the 50 copy HIV-RNA endpoint showed responses of 38% for ATV/r and 46% for LPV/r at week 48; the ATV/r arm was 8% inferior to LPV/r at week 48, with 95% confidence intervals of −20.4% to +4.4%. These 95% confidence intervals fall outside the 10–12% limits that would normally be used to define equivalent or non-inferior efficacy.

Intent-to-treat analyses in open-label trials typically include only those patients who receive at least one dose of study drug; patients who are randomly assigned but are never treated are normally excluded from this type of analysis (intent-to-treat exposed method). Of the patients randomly assigned to the BMS-045 trial, five patients in the LPV/r arm but only one patient in the ATV/r arm were assigned but never treated. Those untreated patients had been included as non-responders in the published results. If an intent-to-treat exposed analysis is conducted, including only patients who received study medication, the percentage with HIV RNA less than 50 copies/ml at week 48 would be 38% for the ATV/r arm versus 48% for LPV/r, a difference of 9.6% (95% confidence intervals −22.1 to +2.8%). Differences in efficacy between arms in the region of 8–10% have been found to be statistically significant in larger randomized clinical trials, as shown in Table 1 [1,3,4].

Although the results from the as-treated analyses show more similar findings for the two arms, the discontinuation rate in the ATV/r arm (22%) is higher than for the LPV/r arm (11%), and it is not clear what proportion of patients withdrew with detectable versus undetectable HIV-RNA levels across the treatment arms.

The primary efficacy endpoint for the BMS-045 trial was the $\log_{10}$ reduction in HIV RNA using a time-averaged difference (TAD) method. This method has been used for the analysis of other trials in treatment-experienced

Table 1. Trial sample size and significance of differences between treatment arms.

Trial	BMS-045	Gilead 934	ACTG 5095
Treatment	ATV/r	ZDV/3TC/EFV	ZDV/3TC/ABC
Arms	LPV/r	TDF/FTC/EFV	ZDV/3TC/(ABC)/EFV
Sample size per arm	120 123	254 255	754 382
Response rates	38 vs 46%	80 vs 88%	79 vs 89%
HIV RNA < 50	(38 vs 48%)[a]		
Difference between arms	8–9.6%	8%	10%
P value	n.s.	0.038	< 0.001
Reference	[1]	[4]	[3]

ABC, Abacavir; ATV/r, atazanavir/ritonavir; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; TDF, tenofovir DF; 3TC, lamivudine; ZDV, zidovudine.
[a]Figures in brackets show results from intention-to-treat exposed analysis.

patients in which rates of HIV-RNA undetectability are expected to be low (for example the TORO clinical trials of enfuvirtide). However, for more recent Food and Drug Administration product labels, the $\log_{10}$ reduction in HIV RNA by TAD is no longer included in the summary of treatment efficacy [5].

There are two main problems with using $\log_{10}$ reductions in HIV RNA to compare treatment groups. First, when a significant proportion of treated patients show HIV-RNA reductions under the assay detection limit, the $\log_{10}$ reduction cannot easily be measured because the lower detection limit has already been achieved: this will tend to make treatment groups appear more similar. Second, there are not standardized methods for including data from early withdrawals. With the TAD method quoted in the report, it is not apparent what assumptions are made for patients who withdraw prematurely or have missing data. A patient who withdraws with undetectable HIV-RNA levels might have these values carried forward, censored, or reset at a zero change from baseline.

In summary, the question remains whether the study's conclusion that ATV/r is as effective as LPV/r is truly describing the overall efficacy of the treatment arms, or is the conclusion rather a result of the chosen statistical analysis in conjunction with a relatively small sample size for a study of this type?

Andrew Hill, *Department of Pharmacology, University of Liverpool, Liverpool, UK.*

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