Immune reconstitution disease associated with parasitic infections following antiretroviral treatment

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SUMMARY

HIV-associated immune reconstitution disease (IRD) is the clinical presentation or deterioration of opportunistic infections that results from enhancement of pathogen-specific immune responses among patients responding to antiretroviral treatment (ART). The vast majority of reported cases of IRD have been associated with mycobacterial, chronic viral and invasive fungal infections; such cases result from dysregulated augmentation of cell-mediated type 1 cytokine-secreting host immune responses. However, the spectrum of infections now recognized as associated with IRD is expanding and includes a number of parasitic infections, which may be mediated by different immunopathological mechanisms. These include leishmaniasis (visceral, cutaneous, mucosal and post kala azar dermal leishmaniasis), schistosomiasis and strongyloidiasis. Since the major burden of HIV lies in resource-limited countries where access to ART is now rapidly expanding, increased awareness and knowledge of these phenomena is important. Here we review the clinical spectrum and pathogenesis of IRD associated with parasitic infections.

Keywords antiretroviral treatment, HAART, HIV, immune reconstitution inflammatory syndrome, immune reconstitution, immune restoration, IRIS, parasitic infection, tropical infection

INTRODUCTION

HIV-associated morbidity and mortality has dramatically decreased in many high-income countries since the advent of antiretroviral treatment (ART) in the mid 1990s (1–3). Robust suppression of viral replication by ART permits both quantitative and functional reconstitution of the immune system (4–6). As a result, primary and secondary prophylaxis for many opportunistic infections that occur among those with advanced immunodeficiency can often be discontinued (7). However, the initial rapid phase of immune recovery may also directly result in adverse clinical phenomena. Previously subclinical infections may be ‘unmasked’ or pre-existing partially treated opportunistic infections may clinically deteriorate (8–10). Such phenomena are believed to arise from a dysregulated augmentation of the host inflammatory response to these infections. Various terms have been used to refer to this, including ‘immune reconstitution syndrome’, ‘immune restoration disease’, and the ‘immune reconstitution inflammatory syndrome’ (familiarly abbreviated to ‘IRIS’). In this review we have used the term ‘immune reconstitution disease’ (IRD).

IRD is not a new phenomenon, but has long been recognized as a complication occurring among patients with severe immunosuppression in whom immune function is rapidly restored. Thus, for example, IRD may occur following withdrawal or rapid dosage reduction of corticosteroid treatment and among patients in whom the blood neutrophil count recovers following cytotoxic chemotherapy or bone marrow transplantation (11). The pathogens involved in IRD reflect the spectrum of opportunistic infections associated with the specific form of immunosuppression. For example, IRD following recovery from neutropenia is typically associated with fungal and pyogenic infections (11).
The vast majority of cases of IRD associated with ART have been reported from high-income countries and have been associated with a wide range of non-parasitic opportunistic infections, including: (a) bacteria (Mycobacterium tuberculosis, Mycobacterium avium complex and other non-tuberculous mycobacteria); (b) viruses (cytomegalovirus, varicella zoster virus, herpes simplex virus, human herpes virus-8, hepatitis B and C and JC virus); and (c) fungi (Pneumocystis jirovecii, Cryptococcus neoformans and Histoplasma spp.) (8–10). However, the spectrum of infections recognized to be associated with IRD continues to increase and case reports now describe IRD associated with some parasitic infections (vide infra).

The majority of people with HIV/AIDS live in resource-limited countries and in June 2005 WHO estimated that 6·5 million people living in such countries were in urgent need of ART (12). Despite formidable logistical challenges, access to ART is now expanding. However, patients in resource-limited settings typically enter ART programmes with advanced symptomatic disease and very low blood CD4 cell counts (13,14). This predisposes them to high rates of both clinical and subclinical opportunistic infections that may potentially be associated with IRD. To date, IRD associated with tuberculosis and cryptococcosal meningitis is reported to be associated with the greatest burden of morbidity and mortality in sub-Saharan Africa (13,15). However, the prevalence of chronic parasitic infections is very high in these populations and yet very little is known about whether these infections may either be associated with IRD or may perhaps modulate immune responses involved in IRD associated with other pathogens. In this paper we review what is currently known about the clinical manifestations and pathogenesis of IRD associated with parasitic infections.

DEFINITION OF IRD
IRD can be defined as the clinical presentation or deterioration of opportunistic infections that results from enhancement of pathogen-specific immune responses among patients responding to ART. However, diagnosis in practice is not straightforward, being one of clinical judgement based on various lines of indirect evidence. These may include: (a) the clinical manifestation or pattern of progression of an opportunistic infection that is unusual; (b) a temporal relationship with ART initiation; (c) exclusion of alternative explanations; (d) demonstrated efficacy of ART (e.g. reduction in viral load or rise in CD4 cell count; (e) evidence of improved CD4 cell function (e.g. development of a positive tuberculin skin test); and (f) histopathology consistent with the diagnosis. Competing explanations for these clinical manifestations that should be excluded are the occurrence of opportunistic infections as a result of residual immunodeficiency and inadequate treatment of an opportunistic infection, including that resulting from drug resistance.

IMMUNOLOGICAL EFFECTS OF ART
Successful ART is associated with a rapid (> 90%) reduction in plasma viral load within the first weeks of ART. The most characteristic immunological feature of HIV infection is depletion of CD4 T cell numbers, and restoration of the CD4 cell subset during ART appears to occur in two principal phases. The initial rapid phase of CD4 cell recovery can usually be detected within the first 1–2 weeks of starting treatment and extends over 2–3 months (4,5). Data suggest that this phase largely represents a redistribution of activated CD4\(^{+}\)CD45RO\(^{+}\) memory cells previously sequestered in lymphoid tissue and a reduction in apoptotic cell death (4,5,16,17). Those with the greatest pretreatment viral loads and CD4 decline have the greatest rates of phase 1 CD4 cell count recovery (18–21). A slower second phase of CD4 cell expansion persists for 1–2 years with variable smaller increments occurring thereafter. This second thymus-dependent phase is associated with expansion of naïve CD45RA\(^{+}\)CD62L\(^{+}\) cells (4,22).

The increase in circulating CD4 cell numbers is also associated with an improvement in effector function, the extent of which is directly related to the degree of viral load suppression and the CD4 cell counts in the longer term (6). IL-2-mediated T lymphocyte proliferative responses to recall antigens are restored (23,24). A switch from type 2 to type 1 cytokine profiles in T lymphocyte stimulation assays and in tissues is detectable early in treatment, with increases in IFN-\(\gamma\) and IL-2 production in response to antigen (25,26). There is diversification of the pathogen-specific T cell receptor repertoire (27,28) and delayed-type hypersensitivity responses to antigens assessed by skin testing are restored (24,29).

Although HIV is principally characterized by CD4 cell depletion, functional deficits in other cells of the innate and acquired immune systems also occur. However, the literature concerning effects of ART on other cell types is much less comprehensive than that concerning CD4 cell reconstitution. Moreover, many of these effects are CD4 cell-dependent, so that attributing ART-induced improvements in immune function to either CD4 cells or to other cell types is difficult.

Decreased macrophage function, including impaired chemotaxis, binding of microorganisms, phagocytosis, antigen processing, microbicidal activity and capacity to secrete interleukin-12 is recognized (30–34). However, data on the impact of ART on these functions are lacking. Dendritic cells (DC) in their role as antigen-presenting cells exert a substantial influence on the phenotype of the subsequent acquired immune response. Both plasmacytoid (pDC) and myeloid (mDC) subsets are reduced in numbers in HIV infection. During ART there is evidence that the defect in
pDC is only partially reversible (35,36), whereas the mDC subset appears better reconstituted by ART (35–37). This differential recovery is of interest when considering IRD because the mDC subset is responsible for polarizing acquired response towards type 1 responses. Reduced CD4⁺ T cell counts are also associated with decreased circulating CD3⁺/CD16⁺/CD56⁺ NK cells (38), however, ART does not appear to be associated with an increase in NK cell function (38–41).

CD8 activation (as determined by co-expression of CD38 and HLA-DR) decreases during ART (4,16,22), probably reflecting to a large extent the reduction in HIV-specific CD8 response that accompanies the reduction in antigen load (42). However, CD8-mediated responses to CMV, for example, improve in the context of an expanding T cell repertoire (28), an effect which appears CD4 cell dependent (43).

The apparent marked dysregulation of the immune response that characterizes IRD suggests that T regulatory cell function may be an important factor in the development of IRD. An inhibitory effect on the ability of DC to mature from peripheral monocytes has been attributed to the presence of HIV-induced CD4⁺ CD25⁺ IL-10-secreting T regulatory cells (44). In addition regulatory T cells are present at higher frequency in the tonsillar tissue of untreated patients than in tissue from those receiving ART (45). It is possible that decreased T regulatory cell function during ART may enable mDC to polarize the acquired immune response towards type 1, thereby favouring development of IRD.

HIV infection is associated with polyclonal B cell activation and defective specific antibody responses (46) and ART is associated with a reduction in risk of serious bacterial infections (e.g. pneumococcal disease) in which immunity is antibody-dependent (47). Furthermore, ART improves the antibody response following vaccination or revaccination, although restoration is not always complete (48,49). There is very little information, however, about the effect of ART on eosinophil numbers and on either specific or total IgE responses that may be relevant to development of IRD in association with helminth infections.

IMMUNOLOGICAL MECHANISMS OF IRD

IRD is most likely to develop in association with those infections for which immune responses are markedly suppressed by HIV and rapidly restored during ART. It occurs most frequently among patients with nadir CD4 cell counts < 50 cells/μL (8,10) who frequently have either subclinical infections or suppressed responses to clinical disease and yet also retain capacity for rapid increments in immune function (21). IRD results from exaggerated host inflammatory responses to soluble antigen, live organisms (in the case of subclinical or partially treated infections) or dead organisms (in the case of treated infections) (8,10,15). It is also recognized that antigen may persist on DC for long periods, a phenomenon recently demonstrated in vivo for HIV antigen despite successful ART (50). When viable organisms are present, it may be difficult to distinguish between IRD and active opportunistic infection, including that resulting from drug resistance. Whilst antigen concentration is likely to influence the risk and severity of IRD, this has not been formally studied.

The vast majority of cases of IRD develop in the first 3 months of ART (8,10), corresponding to the first phase of immune reconstitution in which there is a very rapid increase in both the number of circulating of CD45RO⁺ memory cells as well as CD4 cell function (4). The extent of sequestration of activated CD45RO⁺ memory cells in lymphoid tissue may be directly related to the HIV load, which would explain why those with the greatest pretreatment viral loads have the greatest phase 1 rates of CD4 cell recovery during ART (18,19) and the greatest risk of IRD (51,52). Recirculation of this previously sequestered cell population may provide the opportunity for relevant pathogen-specific cells to gain access to sites of infection and engage in the host inflammatory response to foreign antigen. IRD can develop within the first 1–2 weeks of ART even prior to any detectable increase in circulating CD4 cell numbers, and this is likely to reflect rapid improvements in immune function.

Most cases of IRD are associated with chronic bacterial infections, viral infections and deep fungal infections, which typically trigger immunopathology via cell-mediated T-helper type 1 (Th1) cytokine-secreting immune responses (8,10,53). Much of our knowledge about the mechanisms of IRD comes from study of cases of mycobacterial IRD (10). Development of IRD coincides with restoration of T lymphocyte proliferative responses, IFN-γ secretion and cell-mediated immune responses to mycobacteria, leading to restoration of delayed type hypersensitivity skin test responses to mycobacterial antigens (29,54,55). These processes are associated with expansion in the number of antigen-specific T cells during IRD (53). Reports of hypercalcaemia (resulting from autologous production of 1,25 dihydroxycholecalciferol) as a manifestation of mycobacterium-associated and cryptococcal IRD also provide evidence of restoration of the physiological function of granulomas (56,57). As might be expected, IRD associated with viral infections, such as cytomegalovirus, JC virus, varicella-zoster virus and hepatitis C virus, is associated with restoration of CD8 T cell responses (58–61). However, data regarding mechanisms of IRD associated with other types of opportunistic infections are lacking.

What determines whether a patient develops immune responses that effectively clear infection vs. responses that lead to the development of florid immunopathology is not clear. It is perhaps the rapidity with which cell-mediated immune responses are restored and a lack of compensating immunoregulatory mechanisms may lead to the uncontrolled
tissue-damaging responses that characterize IRD. In this respect, it has been speculated that some patients may have a genetically determined immunological predisposition to development of IRD (62). It is hypothesized that polymorphisms in cytokine genes may influence the rate of clearance of opportunistic pathogens or may cause dysregulation of the inflammatory response. Association of such polymorphisms with development of IRD has been described in small groups of patients developing IRD associated with a range of organisms (62). However, whether mechanistic relationships exist has yet to be demonstrated.

IRD ASSOCIATED WITH PARASITIC INFECTIONS

The number of reports of IRD associated with parasitic diseases is small but increasing (Table 1) and most have been among immigrants to developed countries. Several reasons may underlie this paucity of data. The association of parasitic infections with IRD may be infrequent or may typically be mild or non-specific, leading to lack of recognition. Indeed, many parasitic infections such as schistosomiasis, trypanosomiasis and filariasis have complex systems of immune evasion, permitting these organisms to exist with little or no host inflammatory response (63). Furthermore, most parasitic diseases induce T-helper type 2 cytokine-secreting immune responses, mediated by antibody production and eosinophils. While such responses may be augmented by restoration of appropriate T-helper cell function during ART, the resulting effects on acute inflammatory processes are perhaps less likely to be clinically apparent compared to those resulting from augmentation of type 1 immune responses. Other reasons for the lack of reported cases of IRD associated with parasitic infections may include lack of awareness of health care personnel or lack of facilities in resource-limited settings to establish diagnoses. However, as clinical awareness of the spectrum of IRD increases and experience with ART grows in resource-limited countries, cases may be recognized more frequently.

**Table 1** Reported cases of immune reconstitution disease associated with parasitic infections

| Organism                  | No. of cases | Clinical manifestation                  | Baseline CD4 cell count/µL | Presentation or deterioration | Reference |
|---------------------------|--------------|----------------------------------------|-----------------------------|-------------------------------|-----------|
| *Protozoa*                |              |                                        |                             |                               |           |
| Leishmania infantum       | 2            | Visceral leishmaniasis                 | 186, 15                     | Presentation                  | Berry, 2004 (68) |
| *Leishmania* spp. (unspecified) | 3            | Visceral leishmaniasis                 | 94, 39, 30                  | Presentation                  | Albrecht, 1998 (69) |
| Leishmania braziliensis    | 1            | Cutaneous + mucosal leishmaniasis      | 38                          | Presentation                  | Posada-Vergara, 2005 (74) |
| Leishmania major           | 1            | Uveitis                                | 4                           | Presentation                  | Blanche, 2002 (77) |
| Leishmania infantum        | 1            | Post kala azar dermal leishmanias      | 35                          | Presentation                  | Ridolfo, 2000 (76) |
| Leishmania donovani (presumed) | 1            | Post kala azar dermal leishmanias      | 150                         | Presentation                  | Gilad, 2001 (75) |
| Toxoplasma gondii          | 1            | Cerebral toxoplasmosis                 | 83                          | Presentation                  | Tsambiras, 2005 (86) |
| Helmints                   |              |                                        |                             |                               |           |
| Schistosoma mansoni        | 1            | Eosinophilia                           | 170                         | Presentation                  | Fernando, 2002 (83) |
| Strongyloides stercoralis  | 1            | Fever, eosinophilia and hepatitis      | 32                          | Presentation                  | Kim, 2004 (81) |

**Leishmaniasis**

Visceral disease (VL) is the clinical form of leishmaniasis that has the most substantial geographical overlap with HIV and typically occurs as an opportunistic infection among HIV-infected individuals with CD4 cell counts < 200 cells/µL (64). This overlap is predominantly in southern Europe and the horn of Africa but expansion of the HIV epidemic in India is also likely to result in an increasing number of co-infected individuals there. In both HIV-infected and non-infected patients, large numbers of parasites multiply within phagocytic mononuclear cells and induce a type 2 cytokine response and hypergammaglobulinemia (65). T cell proliferation and IFN-γ production on stimulation with leishmania antigen *in vitro* are typically deficient (66).

Many patients with VL have received ART in southern Europe (67) and yet the number of suspected cases of IRD is very few. It is notable that all six of the possible cases describe the unmasking of subclinical infection following initiation of ART, whereas none of the reports describe clinical deterioration of pre-existing VL (Table 1). Two reports of IRD associated with *L. infantum* VL in southern France describe
asymptomatic patients who developed fever and hepatosplenomegalgy due to VL within the first 2 weeks of initiating ART (68). Another report describes a patient who had not been to a leishmaniasis-endemic area for 8 years and who, following commencement of ART, soon developed fever and thrombocytopenia due to VL (69). A further report describes three patients in Spain who had an excellent virological response to ART and yet developed fever and hepatosplenomegalgy during the initial months of ART (70). However, an important study by de la Rosa et al. suggests that this phenomenon is uncommon (71). They described a series of 11 patients with documented untreated subclinical VL who commenced ART; none developed clinical VL during follow-up (71), suggesting that the risk of development of VL-associated IRD among such patients is low.

Two factors are leading to increased overlap of New World leishmaniasis and HIV infections in South America: a rising prevalence of leishmaniasis in urban areas as well as expansion of the HIV epidemic into rural areas where leishmaniasis is more common. Cutaneous, mucosal and post kala azar dermal leishmaniasis (PKDL) are associated with an intense granulomatous response, causing tissue pathology via a CD4 cell-dependent process (72,73). From a mechanistic viewpoint, one might therefore expect that IRD would be more commonly associated with tegumentary forms of disease rather than VL. However, as yet reports of the former are few.

Two cases of IRD associated with cutaneous and mucosal leishmaniasis have been reported from Brazil (Table 1) (74). One patient, who had left an area endemic for leishmaniasis 15 years earlier, developed progressive cutaneous papules, plaques and ulcers and also ulceration of the oronasopharyngeal mucosa after initiating ART. The second HIV-infected patient presented with multiple cutaneous leishmaniasis lesions, which deteriorated markedly 1 month after starting ART and which were also accompanied by development of oronasopharyngeal lesions. Diagnoses of disease due to Leishmania braziliensis were established in both patients and both responded well to treatment with either amphotericin B or pentavalent antimony (74).

Two cases of PKDL presenting as IRD have been reported from Israel (75) and Italy (76). An Ethiopian immigrant to Israel who had been treated for VL some years earlier developed the typical cutaneous lesions of PKDL over the face and torso 2 weeks after initiating ART (75). The diagnosis was histologically confirmed. The other case was an HIV-infected patient who was initially treated for VL and then developed PKDL on her lower limbs 6 months after commencing ART (76). However, a diagnosis of IRD in this latter case cannot be strongly justified and the presentation may simply represent the normal presentation of PKDL.

A further patient with diffuse cutaneous leishmaniasis in France treated successfully with amphotericin B developed severe bilateral granulomatous anterior uveitis 4 months after starting ART (77). Treatment with liposomal amphotericin B and interferon-γ (IFN-γ) failed to control the disease and one eye had to be enucleated. Histological examination revealed florid inflammation and the presence of amastigotes. A further similar case of fulminant ocular leishmaniasis due to Leishmania donovani during ART has been reported from the Netherlands (78). Histological examination of the enucleated eye revealed massive granulomatous infiltrates throughout the eye but the distinction between active infection and IRD was unclear.

**Strongyloidiasis**

The lack of an association between HIV-related immuno-deficiency and risk of disseminated strongyloidiasis has been intriguing (79). A possible explanation for this is suggested by data reported by Viney et al., who demonstrated that progressive HIV-associated CD4 lymphocytopenia was associated with diminishing likelihood of larval maturation within the gut. Decreased larval maturation would diminish the risk of autoinfection – a process required in the development of hyperinfection (80). However, two cases of possible IRD involving disseminated strongyloidiasis have now been reported, representing a new and unexpected interaction (81,82). Both were in immigrants from low-income to high-income countries and presented within the first weeks of ART. The first case developed fever, eosinophilia and hepatitis (81); the second patient presented with gastrointestinal symptoms and pruritis, and investigations revealed pulmonary radiographic infiltrates and eosinophilia (82). Numerous larvae of Strongyloides stercoralis were found in stool specimens from both patients and both responded well to antihelminthic treatment. Both cases were temporally related to the commencement of ART.

It is not clear whether these cases arose due to the triggering of immune responses to pre-existing disseminated infection in these patients or whether immune recovery facilitated dissemination of strongyloidiasis. Of note, the first case had recently received corticosteroids as a component of treatment for cerebral toxoplasmosis and this would have served as a potent stimulus for dissemination of the strongyloides infection prior to starting ART.

**Schistosomiasis**

Two cases of schistosomiasis-associated IRD have been reported (Table 1) (83,84). The first report describes an African immigrant to the UK who was found to be HIV-infected and to have hepatosplenomegalgy. The baseline eosinophil count was normal but this increased 1 month after initiating ART and peaked at $1.5 \times 10^9$ cells/L after 4 months of treatment. The hepatosplenomegalgy was proven by biopsy to be due to ...
Schistosoma mansoni infection and the patient was treated with praziquantel, leading to a reduction in eosinophil count. No clinical manifestations accompanied the eosinophilia and so this might be better termed an immune reconstitution ‘phenomenon’ rather than ‘disease’. The second report described a South African man who emigrated to the UK and 14 years later commenced ART (84). Treatment was stopped and reinitiated on five occasions due to development of vomiting, diarrhoea and abdominal pain. Symptoms developed within the first few weeks of treatment on each occasion. Colonoscopy revealed patchy inflammation of the large bowel and mucosal biopsies showed florid eosinophilic granulomatous inflammation associated with both viable and dead eggs of S. mansoni. No comment was made on whether the episodes were associated with peripheral blood eosinophilia. Subsequent treatment for schistosomiasis led to resolution of symptoms.

Disease associated with schistosomiasis is mediated by eosinophilic granulomatous inflammation associated with ova. As with the cases of strongyloidosis-associated IRD, enhancement of T helper type 2 responses may have exacerbated eosinophilic inflammation in both of these cases. If schistosoma eggs antigens were responsible for triggering the immune-mediated inflammation within the intestinal wall in the case described by de Silva et al (84), it is intriguing that symptoms were resolved following praziquantel treatment, which would not have affected the existing egg antigen burden within the intestinal mucosa.

Large numbers of patients have received ART in east Africa where the prevalence of schistosomiasis is high and yet no reports of schistosomiasis-associated IRD have emerged from the region. Awareness of this potential complication of ART may lead to recognition of further cases.

Other parasites

Just two cases of suspected IRD associated with toxoplasma encephalitis have been reported in published literature. In one case no clinical details were given (85). In the other, an HIV-infected patient with a nadir CD4 cell count of 83 cells/μL presented with a focal seizure after 3 weeks of ART (86). This was diagnosed as cerebral toxoplasmosis on the basis of positive serology, multiple ring-enhancing intracerebral lesions on a magnetic resonance imaging scan and a positive response to treatment for toxoplasmosis. Toxoplasmosis is a common end-stage opportunistic infection in industrialized countries for which ART is often initiated fairly early. The fact that more cases have not been reported casts some doubt on whether this infection may be associated with IRD.

There are no reports in the literature of IRD associated with helminthic or protozoal infections other than those described above. However, an important question is whether malaria may be associated with IRD. Although large numbers of individuals have received ART in sub-Saharan African countries where Plasmodium falciparum malaria is hyperendemic, no cases of malaria-associated IRD have been reported. The likeliest manifestation, however, might be very non-specific such as development of fever; it seems unlikely that severe manifestations would arise.

CONCLUSIONS

IRD associated with infections has emerged as an important cause of morbidity complicating the initial months of ART. As access to ART is scaled up in many low-income countries, the extent to which IRD will contribute to morbidity and mortality in treatment programmes has yet to be determined. However, as patients typically present to ART services with marked lymphocytopenia and frequent co-infections, IRD is likely to be common. Most IRD results from dysregulated augmentation of cell-mediated immune responses to mycobacterial, chronic viral and invasive fungal infections. However, the spectrum of infections recognized to be associated with IRD now encompasses a number of parasitic diseases, including leishmaniasis (visceral, cutaneous, mucosal and PKDL), schistosomiasis and strongyloidiasis. No studies have yet examined the mechanisms of IRD associated with helminth infections, but these may be due to augmentation of appropriate type 2 immune responses. More research is needed to increase our understanding of these emerging phenomena.

ACKNOWLEDGEMENTS

SDL and RJW are both funded by the Wellcome Trust, UK with grant numbers 074641/Z/04/Z (SDL) and 072070 (RJW).

REFERENCES

1 Egger M, May M, Chene G et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 2002; 360: 119–129.
2 Palella FJ Jr, Delaney KM, Moorman AC et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998; 338: 853–860.
3 Mocroft A, Vella S, Benfield TL et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998; 352: 1725–1730.
4 Autran B, Careelain G, Li TS et al. Positive effects of combined antiretroviral therapy on CD4+ T-cell homeostasis and function in advanced HIV disease. Science 1997; 277: 112–116.
5 Careelain G, Dhebre P & Autran B. Reconstitution of CD4+ T lymphocytes in HIV-infected individuals following antiretroviral therapy. Curr Opin Immunol 2001; 13: 483–488.
6 Lederman MM. Immune restoration and CD4+ T-cell function with antiretroviral therapies. AIDS 2001; 15 (Suppl. 2): S11–S15.
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7 Kirk O, Reiss P, Uberti-Foppa C et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med* 2002; 137: 239–250.

8 Shelburne SA III & Hamill RJ. The immune reconstitution inflammatory syndrome. *AIDS Rev* 2003; 5: 67–79.

9 French MA, Price P & Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS* 2004; 18: 1615–1627.

10 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.

11 Cheng VC, Yuen KY, Wong SS et al. Immuno-restitution diseases in patients not infected with HIV. *Eur J Clin Microbiol Infect Dis* 2001; 20: 402–406.

12 WHO/UNAIDS. Progress of global access to HIV antiretroviral therapy. An update on ‘3 by 5’. June 2005. http://www.who.int/hiv/pub/progressreports/3bys5/20Report_E_light.pdf. Accessed 19.10.05.

13 Lawn SD, Myer L, Orrell C et al. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS* 2005; 19: 2141–2148.

14 Cobbolds R, Ronald A, Katabira E et al. Rolling out antiretrovirals in Africa: there are still challenges ahead. *Clin Infect Dis* 2005; 41: 386–389.

15 Lawn SD, Bekker LG, Myer L et al. Cryptococcal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. *AIDS* 2005; 19: 2050–2052.

16 Evans TG, Bonnez W, Soucie HR et al. Highly active antiretroviral therapy results in a decrease in CD8+ T cell activation and preferential reconstitution of the peripheral CD4+ T cell population with memory rather than naive cells. *Antiviral Res* 1998; 39: 163–173.

17 Chavan SJ, Tamma SL, Kaplan M et al. Reduction in T cell apoptosis in patients with HIV disease following antiretroviral therapy. *Clin Immunol* 1999; 93: 24–33.

18 Le Moing V, Thiebaut R, Chen G et al. Predictors of long-term increase in CD4 (+) cell counts in human immunodeficiency virus-infected patients receiving a protease inhibitor-containing antiretroviral regimen. *J Infect Dis* 2002; 185: 471–480.

19 Bennett KK, DeGruittola VG, Marschner IC et al. Baseline predictors of CD4 T-lymphocyte recovery with combination antiretroviral therapy. *J Acquir Immune Defic Syndr* 2002; 31: 20–26.

20 Renaud M, Katlama C, Mallet A et al. Determinants of paradoxical CD4 cell reconstitution after protease inhibitor-containing antiretroviral regimen. *AIDS* 1999; 13: 669–676.

21 Lawn SD, Myer L, Bekker LG et al. CD4 cell count recovery among HIV-infected patients with very advanced immunodeficiency commencing antiretroviral treatment in sub-Saharan Africa. *BMC Infect Dis* 2006; 6: 59.

22 Landay AL, Bettendorf D, Chan E et al. Evidence of immune reconstitution in antiretroviral drug-experienced patients with advanced HIV disease. *AIDS Res Hum Retroviruses* 2002; 18: 95–102.

23 Valdez H, Smith KY, Landay A et al. Response to immunization with recall and neoantigens after prolonged administration of an HIV-1 protease inhibitor-containing regimen. ACTG 375 team. *AIDS Clinical Trials Group. AIDS* 2000; 14: 11–21.

24 Wendland T, Furrer H, Vernazza PL et al. HAART in HIV-infected patients: restoration of antigen-specific CD4 T-cell responses in vitro is correlated with CD4 memory T-cell reconstitution, whereas improvement in delayed type hypersensitivity is related to a decrease in viraemia. *AIDS* 1999; 13: 1857–1862.

25 Hardy GA, Imami N, Sullivan AK et al. Reconstitution of CD4+ T cell responses in HIV-1 infected individuals initiating highly active antiretroviral therapy (HAART) is associated with renewed interleukin-2 production and responsiveness. *Clin Exp Immunol* 2003; 134: 98–106.

26 Imami N, Antonopoulos C, Hardy GA et al. Assessment of type 1 and type 2 cytokines in HIV type 1-infected individuals: impact of highly active antiretroviral therapy. *AIDS Res Hum Retroviruses* 1999; 15: 1499–1508.

27 Gorochov G, Neumann AU, Kereveur A et al. Perturbation of CD4+ and CD8+ T-cell repertoires during progression to AIDS and regulation of the CD4+ repertoire during antiviral therapy. *Nat Med* 1998; 4: 215–221.

28 Worrell S, Deayton J, Hayes P et al. Molecular correlates in AIDS patients following antiretroviral therapy: diversified T-cell receptor repertoires and in vivo control of cytomegalovirus replication. *HIV Med* 2001; 2: 11–19.

29 French MA, Mallal SA & Dawkins RL. Zidovudine-induced restoration of cell-mediated immunity to mycobacteria in immunodeficient HIV-infected patients. *AIDS* 1992; 6: 1293–1297.

30 Crowe SM, Vardaxis NJ, Kent SJ et al. HIV infection of monocyte-derived macrophages in vitro reduces phagocytosis of Candida albicans. *J Leukoc Biol* 1994; 56: 318–327.

31 Gazzinelli RT, Bala S, Stevens R et al. HIV infection suppresses type 1 lymphokine and IL-12 responses to Toxoplasma gondii but fails to inhibit the synthesis of other parasite-induced monokines. *J Immunol* 1995; 155: 1565–1574.

32 Imperioli FG, Zaninoni A, La Maestra L et al. Increased Mycobacterium tuberculosis growth in HIV-infected human macrophages: role of tumour necrosis factor-alpha. *Clin Exp Immunol* 2001; 123: 435–442.

33 Baldwin GC, Fleischmann J, Chung Y et al. Human immunodeficiency virus causes mononuclear phagocyte dysfunction. *Proc Natl Acad Sci USA* 1990; 87: 3933–3937.

34 Smith PD, Ohura K, Masur H et al. Monocyte function in the acquired immune deficiency syndrome. Defective chemotaxis. *J Clin Invest* 1984; 74: 2121–2128.

35 Finke JS, Shodell M, Shah K et al. Dendritic cell numbers in the blood of HIV-1 infected patients before and after changes in antiretroviral therapy. *J Clin Immunol* 2004; 24: 647–652.

36 Chehimi J, Campbell DE, Azzoni L et al. Persistent decreases in blood plasmacytoid dendritic cell number and function despite effective highly active antiretroviral therapy and increased blood myeloid dendritic cells in HIV-infected individuals. *J Immunol* 2002; 168: 4796–4801.

37 Barron MA, Blyveis N, Palmer BE et al. Influence of plasma viremia on defects in number and immunophenotype of blood dendritic cell subsets in human immunodeficiency virus 1-infected individuals. *J Infect Dis* 2003; 187: 26–37.

38 Douglas SD, Durako SJ, Tustin NB et al. Natural killer cell enumeration and function in HIV-infected and high-risk uninfected adolescents. *AIDS Res Hum Retroviruses* 2001; 17: 543–552.

39 Parato KG, Kumar A, Badley AD et al. Normalization of natural killer cell function and phenotype with effective anti-HIV therapy and the role of IL-10. *AIDS* 2002; 16: 1251–1256.
Vogler MA, Teppler H, Gelman R et al. Daily low-dose subcutaneous interleukin-2 added to single- or dual-nucleoside therapy in HIV infection does not protect against CD4+ T-cell decline or improve other indices of immune function: results of a randomized controlled clinical trial (ACTG 248). J Acquir Immune Defic Syndr 2004; 36: 576–587.

Azzoni L, Papasavvas E, Chehim J et al. Residual HIV-specific CD4 and CD8 T cell frequencies after prolonged antiretroviral therapy reflect pretreatment plasma virus load. AIDS 2002; 16: 2317–2322.

Kharbanda M, Than S, Chitnis V et al. Patterns of CD8 T cell clonal dominance in response to change in antiretroviral therapy in HIV-infected children. AIDS 2000; 14: 2229–2238.

Carbonneil C, Donkova-Petrvini V, Aouba A et al. Defective dendritic cell function in HIV-infected patients receiving effective highly active antiretroviral therapy: neutralization of IL-10 production and depletion of CD4+CD25+ T cells restore high levels of HIV-specific CD4+ T cell responses induced by dendritic cells generated in the presence of IFN-alpha. J Immunol 2004; 172: 7832–7840.

Andersson J, Boasso A, Nilsson J et al. The prevalence of regulatory T cells in lymphoid tissue is correlated with viral load in HIV-infected patients. J Immunol 2005; 174: 3143–3147.

De Milito A. B lymphocyte dysfunctions in HIV infection. Curr HIV Res 2004; 2: 11–21.

Grau J, Pallares R, Tubau F et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. Arch Intern Med 2005; 165: 1533–1540.

Yamanaka H, Teruya K, Tanaka M et al. Efficacy and immunologic responses to influenza vaccine in HIV-1-infected patients. J Acquir Immune Defic Syndr 2005; 39: 167–173.

Rimland D & Guest JL. Response to hepatitis A vaccine in HIV patients in the HAART era. AIDS 2005; 19: 1702–1704.

Popovic M, Tenner-Racz K, Pelzer C et al. Persistence of HIV-1 structural proteins and glycoproteins in lymph nodes of patients under highly active antiretroviral therapy. Proc Natl Acad Sci USA 2005; 102: 14807–14812.

Narita M, Ashkin D, Hollender ES et al. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am J Respir Crit Care Med 1998; 158: 157–161.

Ohalla J, Pulido F, Rubio R et al. Paradoxical responses in a cohort of HIV-1-infected patients with mycobacterial disease. Int J Tuberc Lung Dis 2002; 6: 71–75.

Bourgarit A, Careljan G, Martinez V et al. Explosion of tuberculosis-specific Th1–responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. AIDS 2006; 20: F1–F7.

Foudraine NA, Hovenkamp E, Notermans DW et al. Immunopathology as a result of highly active antiretroviral therapy in HIV-1-infected patients. AIDS 1999; 13: 177–184.

Havlir DV, Schrier RD, Torriani FJ et al. Effect of potent antiretroviral therapy on immune responses to Mycobacterium avium in human immunodeficiency virus-infected subjects. J Infect Dis 2000; 182: 1658–1663.

Lawn SD & Macallan DC. Hypocalcaemia: a manifestation of immune reconstitution complicating tuberculosis in an HIV-infected person. Clin Infect Dis 2004; 38: 154–155.

Jenny-Avital ER & Abadi M. Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. Clin Infect Dis 2002; 35: e128–e133.

Mutimer HP, Akatsuka Y, Manley Y et al. Association between immune recovery uveitis and a diverse intraocular cytomegalovirus-specific cytotoxic T cell response. J Infect Dis 2002; 186: 701–705.

Miralles P, Berenguer J, Lacruz C et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after highly active antiretroviral therapy. AIDS 2001; 15: 1900–1902.

Martinez E, Gatell J, Moran Y et al. High incidence of herpes zoster in patients with AIDS soon after therapy with protease inhibitors. Clin Infect Dis 1998; 27: 1510–1513.

Zylberberg H, Pialoux G, Carnot F et al. Rapidly evolving hepatitis C virus-related cirrhosis in a human immunodeficiency virus-infected patient receiving triple antiretroviral therapy. Clin Infect Dis 1998; 27: 1255–1258.

Price P, Morahan G, Huang D et al. Polyomaviruses in cytotoxic genes define subpopulations of HIV-1 patients who experienced immune restoration diseases. AIDS 2002; 16: 2043–2047.

Gupta S. Parasite immune escape: new views into host–parasite interactions. Curr Opin Microbiol 2005; 8: 428–433.

Olivier M, Badaro R, Medrano FJ et al. The pathogenesis of Leishmaniala/HIV co-infection: cellular and immunological mechanisms. Ann Trop Med Parasitol 2003; 97 (Suppl. 1): 79–98.

Zwingerkererberg K, Harms G, Pedrosa C et al. Determinants of the immune response in visceral leishmaniasis: evidence for predominance of endogenous interleukin 4 over interferon-gamma production. Clin Immunol Immunopathol 1990; 57: 242–249.

Carvalho EM, Bacellar O, Brownell C et al. Restoration of IFN-gamma production and lymphocyte proliferation in visceral leishmaniasis. J Immunol 1994; 152: 5949–5956.

Lopez-Velez R. The impact of highly active antiretroviral therapy (HAART) on visceral leishmaniasis in Spanish patients who are co-infected with HIV. Am Trop Med Parasitol 2003; 97 (Suppl. 1): 143–147.

Berry A, Abraham B, Dereure J et al. Two case reports of symptomatic visceral leishmaniasis in AIDS patients concomitant with immune reconstitution due to antiretroviral therapy. Scand J Infect Dis 2004; 36: 225–227.

Albrecht H. Leishmaniosi – new perspectives on an under-appreciated opportunistic infection. AIDS 1998; 12: 2225–2226.

Jimenez-Exposito MJ, Alonso-Villaverde C, Sarda P et al. Visceral leishmaniasis in HIV-infected patients with non-detectable HIV-1 viral load after highly active antiretroviral therapy. AIDS 1999; 13: 152–153.

de la RR, Pineda JA, Delgado J et al. Influence of highly active antiretroviral therapy on the outcome of subclinical visceral leishmaniasis in human immunodeficiency virus-infected patients. Clin Infect Dis 2001; 32: 633–635.

Soong L, Chang CH, Sun J et al. Role of CD4+ T cells in pathogenesis associated with Leishmania amazonensis infection. J Immunol 1997; 158: 5374–5383.

Terabe M, Kuramochi T, Ito M et al. CD4 (+) cells are indispensable for ulcer development in murine cutaneous leishmaniasis. Infect Immun 2000; 68: 4574–4577.

Posada-Vergara MP, Lindoso JA, Tolezano JE et al. Tegumentary leishmaniasis as a manifestation of immune reconstitution inflammatory syndrome in 2 patients with AIDS. J Infect Dis 2005; 192: 1819–1822.

Gidal B, Borer A, Hallely D et al. Post-kala-azar dermal
leishmaniasis manifesting after initiation of highly active anti-retroviral therapy in a patient with human immunodeficiency virus infection. *Isr Med Assoc J* 2001; 3: 451–452.

76 Ridolfo AL, Gervasoni C, Antinori S et al. Post-kala-azar dermal leishmaniasis during highly active antiretroviral therapy in an AIDS patient infected with Leishmania infantum. *J Infect* 2000; 40: 199–202.

77 Blanche P, Gombert B, Rivoal O et al. Uveitis due to *Leishmania major* as part of HAART–induced immune restitution syndrome in a patient with AIDS. *Clin Infect Dis* 2002; 34: 1279–1280.

78 Meenken C, van Agtmael MA, Ten Kate RW et al. Fulminant ocular leishmaniasis in an HIV-1-positive patient. *AIDS* 2004; 18: 1485–1486.

79 Lucas SB. Missing infections in AIDS. *Trans R Soc Trop Med Hyg* 1990; 84 (Suppl. 1): 34–38.

80 Viney ME, Brown M, Omoding NE et al. Why does HIV infection not lead to disseminated strongyloidiasis? *J Infect Dis* 2004; 190: 2175–2180.

81 Kim AC & Lupatkin HC. *Strongyloides stercoralis* infection as a manifestation of immune restoration syndrome. *Clin Infect Dis* 2004; 39: 439–440.

82 Lanzafame M, Faggian F, Lattuada E et al. Strongyloidiasis in an HIV-1-infected patient after highly active antiretroviral therapy-induced immune restoration. *J Infect Dis* 2005; 191: 1027.

83 Fernando R & Miller R. Immune reconstitution eosinophilia due to schistosomiasis. *Sex Transm Infect* 2002; 78: 76.

84 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.

85 Jevtovic DJ, Salemovic D, Ranin J et al. The prevalence and risk of immune restoration disease in HIV-infected patients treated with highly active antiretroviral therapy. *HIV Med* 2005; 6: 140–143.

86 Tsambiras PE, Larkin JA & Houston SH. Case report. Toxoplasma encephalitis after initiation of HAART. *AIDS Read* 2001; 11: 608–606.