

Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals

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Immune reconstitution disease (IRD) in HIV-infected patients is an adverse consequence of the restoration of pathogen-specific immune responses during the initial months of highly active antiretroviral treatment (HAART). Previously subclinical infections are “unmasked” or pre-existing opportunistic infections clinically deteriorate as host immunopathological inflammatory responses are “switched on”. IRD is most frequently associated with mycobacterial infections. Our literature search identified 166 published cases of IRD associated with mycobacterial infections. We review the underlying immunological mechanisms, difficulties surrounding case definition and diagnosis, the wide diversity of clinical manifestations, and treatment. The importance of screening patients for mycobacterial disease before starting HAART and the critical impact of the timing of commencement of HAART in patients receiving treatment for tuberculosis are highlighted. We also discuss the problem of IRD associated with mycobacterial diseases in developing countries where tuberculosis prevalence is high and access to HAART is currently expanding.

Introduction

Mycobacterial opportunistic infections are a major cause of morbidity and mortality among patients living with HIV/AIDS worldwide. *Mycobacterium avium* complex (MAC) is among the most common opportunistic bacterial infections in those with advanced immunodeficiency living in industrialised countries¹ and tuberculosis is the leading cause of morbidity and mortality in those with HIV/AIDS living in low income countries.² A variety of other non-tuberculous mycobacteria, including *Mycobacterium kansasii* and *Mycobacterium xenopi*, are also recognised opportunistic pathogens, principally occurring in late-stage disease. Since the mid 1990s, however, a dramatic decline in HIV-associated morbidity and mortality has been observed in countries where highly active antiretroviral treatment (HAART) has been widely available.^{3,4} Prophylaxis or treatment of many opportunistic infections, including disseminated MAC infection, can be discontinued among patients who have responded to HAART.^{5,6} Several studies have also shown that the incidence of tuberculosis decreases by approximately 70–90% in treated cohorts living in high and low income countries.^{7–10}

The major beneficial effects of HAART result from gradual restoration of pathogen-specific immune responses. However, during the initial months of HAART immune reconstitution is complicated by adverse clinical phenomena in which either previously subclinical infections are “unmasked” or pre-existing partly treated opportunistic infections clinically deteriorate. These clinical phenomena are thought to result from immunopathological host inflammatory responses being “switched on”. Such phenomena have been variously termed immune reconstitution syndrome, immune reconstitution inflammatory syndrome, immune restoration disease, immunorestitution disease, and immune reconstitution phenomena. Here, we use the term immune reconstitution disease (IRD).

IRD is not a new phenomenon, nor is it specific to HIV-infected individuals receiving HAART. Indeed, the

potential for IRD exists whenever patients who have been severely immunocompromised have rapid restoration of immune function. Thus, for example, similar phenomena are recognised following a dosage reduction or withdrawal of steroids and among patients in whom the absolute neutrophil count in the blood recovers following either cytotoxic chemotherapy or bone marrow transplantation.^{11,12} The potential pathogens involved in IRD reflect the spectrum of opportunistic infections associated with the specific form of immunosuppression. For example, fungal and pyogenic infections typically present as IRD following recovery from neutropenia.¹¹

IRD is most frequently reported in patients with HIV infection receiving HAART. In such patients, IRD has been associated with a range of opportunistic infections, including cytomegalovirus, hepatitis B and C viruses, *Pneumocystis carinii*, *Cryptococcus neoformans*, herpesviruses, progressive multifocal leucoencephalopathy (caused by JC virus), leishmaniasis, and cerebral toxoplasmosis.^{13–16} However, mycobacteria are the infections most frequently implicated in IRD, causing approximately 40% of the cases reported up to 2002.¹³

Paradoxical reactions to antimycobacterial treatment

Before considering IRD triggered by HAART, it is important to consider the related phenomenon of paradoxical reactions, which occurs in some patients receiving treatment for certain mycobacterial infections, irrespective of HIV status. Paradoxical reactions are observed among 2–23% of HIV-seronegative patients receiving treatment for tuberculosis^{17–20} and are generally defined as the clinical or radiological deterioration of pre-existing tuberculous lesions or the development of new lesions in patients initially responding to effective treatment. Manifestations of paradoxical reactions may be as subtle as fever and minor lymph node enlargement, or as dramatic as respiratory failure or neurological deterioration.

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Among a prospective series of 104 HIV-seronegative patients treated for tuberculosis in Hong Kong, 16 (15.4%) developed a paradoxical reaction after a median of 56 days (range 20–109 days).²⁰ Similarly, among a retrospective series of 50 HIV-seronegative patients treated for tuberculosis in the UK, paradoxical reactions were observed among five (10%) after a median of 87 days (range 23–157 days).¹⁹ Cheng and colleagues reviewed 120 published cases and found that the paradoxical deterioration occurred after a median of 60 days, developing at the initial site of infection in approximately 75% of cases and new lesions developing at another anatomical site among the remainder.²¹ Extrapulmonary site of disease, especially the central nervous system, is a strong risk factor for paradoxical reactions^{19–21} and management frequently requires additional interventions such as surgery, therapeutic aspiration, and use of corticosteroids.²¹

Paradoxical reactions are thought to be due to intensification of cell-mediated immune responses and may be associated with conversion of pretreatment cutaneous anergy to purified protein derivative (PPD) to a positive response following antituberculosis treatment.²² In those with active tuberculosis, proinflammatory and immunosuppressive immune mechanisms are present concomitantly,²³ the balance of which might be altered during the early stages of antituberculosis treatment. A study of HIV-seronegative patients with advanced pulmonary tuberculosis in South Africa found that additional weight loss and functional deterioration often occurred during the first month of antituberculosis treatment.²⁴ These changes were temporally associated with a rise in the serum concentration of tumour necrosis factor α that was dissociated from other indices of immune activation, and may have resulted from macrophage activation in response to release of mycobacterial cell wall antigens—eg, lipoarabinomannan—during treatment.^{24,25}

Definition and diagnosis of IRD

A precise definition of antiretroviral-associated IRD in HIV-infected patients is difficult to establish. IRD could be defined as the presentation or clinical deterioration of opportunistic infections in HIV-infected patients as a direct result of the enhancement of immune responses to those pathogens during HAART. However, in clinical practice, it may be difficult to either demonstrate or refute a causal relation between starting HAART and development of such clinical phenomena. Competing explanations for these clinical manifestations are that the presentation or deterioration of opportunistic infections arise as a complication of residual immunodeficiency, inadequate treatment, or are paradoxical reactions that would have occurred in the absence of HAART. Thus, various factors have to be evaluated when considering a diagnosis of IRD (panel 1).

The temporal association between commencement of HAART (or change from a previously failing regimen) and the development of an unusual clinical phenomenon often provides a strong clue to the diagnosis of IRD. However, rates of immune restoration are very variable between patients, and it is possible that a bias exists in the reported cases in the literature whereby cases of IRD occurring soon after starting HAART are more readily attributed to IRD than those occurring more remotely. Clinical judgment has a role in evaluating whether or not the presentation and clinical course of the opportunistic infection are unusual. Alternate explanations for the clinical deterioration must be excluded, including lack of compliance with treatment for the opportunistic infection, drug resistance, or development of a new opportunistic infection. Evidence of an improvement in immune function that is temporally associated with the clinical phenomenon may support a diagnosis of IRD. Measurement of in-vitro T-lymphocyte proliferative responses to mycobacterial antigens may provide such information in a research context.²⁶ A more practical test for clinical use is assessment of cutaneous delayed type hypersensitivity (DTH) responses to PPD or MAC antigen.^{18,27,28} Strong DTH responses may support a diagnosis of IRD. However, clinical trials have not formally assessed the role of skin test responses within a diagnostic work up.

Development of IRD is associated with a preceding increase in CD4 lymphocyte count in most patients and this increase may provide support for a diagnosis of IRD. However, a rise in blood CD4 lymphocyte count per se is not direct evidence of improved functional immune responses to the pathogen in question. Conversely, lack of a rise in blood CD4 lymphocyte count does not indicate that there has been no restoration of functional T-lymphocyte responses; some cases of IRD occur within the first 2 weeks of HAART before any rise in blood CD4 lymphocyte count. Thus, although a preceding rise in blood CD4 lymphocyte count is commonly seen in IRD, it is neither a diagnostic, specific, nor essential element in

Panel 1: Factors to be evaluated in considering whether the presentation or deterioration of an opportunistic mycobacterial infection is due to immune reconstitution disease

Temporal association between starting HAART regimen and subsequent development of clinical phenomena (the majority within 3 months).

Unusual clinical manifestations.

Unexpected clinical course.

Exclusion of alternative explanations—eg, drug resistance, non-compliance with treatment for the opportunistic infection.

Evidence of preceding immune restoration—eg, a rise in blood CD4 lymphocyte count; restoration of cutaneous hypersensitivity to mycobacterial antigens (PPD or MAC antigen); increased in-vitro T-cell proliferative responses to PPD or MAC antigen.

Histopathological or cytological appearances of unexpectedly florid cell-mediated immune response within tissue samples.

Preceding fall in plasma HIV-1 load, providing evidence of a response to HAART.

the diagnosis. However, a positive response to antiretrovirals—as reflected by a falling viral load—is invariably seen, and is perhaps an equally or more important indicator.

Identification of serum markers that facilitate the diagnosis of IRD would be useful. However, measurement of serum immunological markers is unlikely to distinguish between opportunistic infections arising because of immunodeficiency and those attributable to IRD. For example, Morlese and colleagues²⁹ suggested that plasma interleukin 6 might be used as a marker of IRD associated with mycobacterial disease. However, interleukin 6 is a proinflammatory cytokine released as part of the host response to a wide variety of pathogens and serum levels are increased in HIV-infected patients with symptomatic tuberculosis irrespective of HAART or IRD.^{24,30} This increase is likely to be true of many other immunological indices too.

HIV and the host response to *Mycobacterium tuberculosis*

IRD associated with mycobacteria is best understood in the context of existing knowledge of host responses to these pathogens and how these are affected by HIV. Following failure of innate immune responses to prevent *Mycobacterium tuberculosis* infection, cell-mediated responses develop. Interleukin 12 and interleukin 2 drive the clonal expansion of CD4 lymphocytes that secrete interferon γ , a potent macrophage activator. Chemokines such as interleukin 8, and proinflammatory cytokines such as tumour necrosis factor α facilitate further mononuclear cell recruitment and activation, respectively.³¹ Development of granulomas provides the critical environment within which the host limits *M tuberculosis* infection.³²

The tuberculous granuloma is characterised by activation and epithelioid differentiation of macrophages and development of multinucleate Langhans' giant cells. CD4 lymphocytes located within the periphery of the granuloma have a critical role in orchestrating cell-mediated immune function. The development of DTH leads to the formation of central caseous necrosis, which inhibits extracellular bacillary growth.³³ However, failure to limit *M tuberculosis* replication results in spreading inflammation and tissue destruction. Subsequent clinical disease is directly attributable to systemic and local tissue-damaging host inflammatory responses to the ongoing presence of the pathogen.³³ Thus, suppression of the host response by HIV co-infection tends to dampen the immunopathology of tuberculosis.

HIV-1 co-infection disrupts cell-mediated immune responses to *M tuberculosis* by impairing both the recruitment and function of the key effector cells involved—namely macrophages and CD4 T lymphocytes.³⁴ Although HIV-1 infection is principally characterised by progressive generalised CD4 lymphopenia, CD4 T lymphocytes are also functionally

impaired. Interleukin 2-mediated CD4 lymphocyte activation and proliferation are inhibited,³⁵ and development of AIDS is associated with increased immunoregulatory and type 2 cytokine secretion and decreased type 1 cytokine secretion. These changes in cytokine secretion drive the humoral arm of the immune system and inhibit cell-mediated immune function.³⁶

By these mechanisms, progressive HIV-associated immunodeficiency results in abrogation of granuloma formation and increased mycobacterial burden in infected tissues. Furthermore, by a variety of mechanisms, immune activation at sites of tuberculosis disease amplifies the local impact of HIV-1 infection.^{34,37} As a result, HIV co-infection alters the clinicopathological features of tuberculosis.³⁴ Attenuation of the host inflammatory response results in diminished tissue damage and increases the likelihood of multibacillary disseminated infection. Thus, patients with AIDS may develop active mycobacterial infection with very high bacillary burden but have few clinical symptoms or signs of disease.

Mechanisms of IRD

The development of HAART using combinations of reverse transcriptase and protease inhibitors in 1995 marked the dawn of a new era in HIV management. For the first time, major reductions in plasma viral load were associated with substantial increases in circulating CD4 lymphocyte numbers and restoration of immune function.^{38–40} The extremely rapid reversal in immune function gives rise to IRD by switching on immunopathological host responses.

A reduction in plasma viral load of more than 90% occurs within the first 1–2 weeks of HAART⁴¹ and associated increases in CD4 lymphocyte counts occur in two principal phases. The initial rapid increase in the number of circulating CD4 lymphocytes can usually be detected within 1–2 weeks of starting treatment and extends over the first 2–3 months of treatment. This increase largely represents a redistribution of activated CD45Ro memory cells previously sequestered in lymphoid tissue and a reduction in apoptotic cell death.^{39,40} A slower second phase of CD4 expansion occurs over subsequent months and may continue for years. This second phase represents expansion of naive CD45Ra cells as thymic function is restored and is largely responsible for the long-term sustained rise in CD4 lymphocyte count.

The majority of reported cases of IRD associated with mycobacteria develop within the first 3 months of HAART^{13,16} when CD45Ro memory lymphocyte redistribution occurs. 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. Antigen that triggers IRD may be in the form of viable organisms, dead organisms, or shed antigen. The fact that mycobacterial organisms

Reference	Previous MAC	Manifestation	ART regimen	Weeks on ART	CD4 count × 10 ⁶ /L		VL copies/mL		Adjunctive interventions
					Baseline	IRD	Baseline	IRD	
Packer ⁵⁹	No	Intrathoracic LN, endobronchial lesion	Zidovudine	8	NS	NS	NS	NS	Surgery
	No	Endobronchial lesion, consolidation	Zidovudine	12	NS	NS	NS	NS	Nil
Barbaro ⁵⁵	No	Submandibular LN	Zidovudine	12	NS	NS	NS	NS	Surgical drainage
	No	Axillary LN	Zidovudine	4	NS	NS	NS	NS	Surgical drainage
	No	Inguinal LN	Zidovudine	8	NS	NS	NS	NS	Surgical drainage
French ²⁷	No	Peripheral, intrathoracic, and intra-abdominal LN; pulmonary	Zidovudine	<2	101	NS	NS	NS	NS
	No	Pulmonary	Zidovudine	<2	209	NS	NS	NS	NS
	No	Cutaneous abscess, axillary LN	Zidovudine	<2	29	NS	NS	NS	NS
	No	Intrathoracic, intra-abdominal LN, hepatitis	Zidovudine	<2	38	NS	NS	NS	NS
Sheppard ⁶⁰	No	Septic arthritis, osteomyelitis	2 NRTI + PI	12	8	98	292 000	800	Surgery
Race ⁶¹	No	Intra-abdominal LN	2 NRTI + PI	1	26	56	NS	NS	ART interrupted
	No	Cervical and intra-abdominal LN	2 NRTI + PI	2-5	9	178	NS	NS	NS
	No	LN (unspecified)	2 NRTI + PI	1-5	39	205	NS	NS	NS
	No	Intra-abdominal LN	2 NRTI	1	25	NS	NS	NS	ART interrupted
Cable ⁵²	No	LN (unspecified)	2 NRTI	3	5	NS	NS	NS	NS
	No	Cervical LN	2 NRTI + PI	6	4	55	119 100	88 200	Surgical drainage
Dworkin ⁵³	No	Cervical LN	2 NRTI + PI	7	70	155	70 400	<LLD	Surgical drainage
	No	Axillary LN	2 NRTI + PI	9	18	>148	258 679	<LLD	Surgery
Bartley ⁶⁰	No	Endobronchial lesion	2 NRTI + PI	2	20	160	450 000	<LLD	Nil
	No	Intrathoracic LN, endobronchial lesion	2 NRTI	12	30	210	410 000	930	Nil
del Giudice ⁴⁷	No	Skin nodules	2 NRTI + PI	4	10	160	500 000	1000	Nil
Boyd ⁶²	No	Psoas abscess	NS	NS	20	243	1200	<LLD	Needle aspiration
	Yes	Psoas abscess	NRTI, NNRTI, PI	24	23	NS	NS	780	Needle aspiration
Phillips ⁵¹	No	Cervical and intrathoracic LN	2 NRTI	2	50	320	NS	↓1.8 log	NS
	No	Inguinal LN	2 NRTI	2	50	70	NS	<LLD	NS
	No	Axillary LN	2 NRTI + PI	4	10	90	NS	↓3.6 log	NS
	No	Supraclavicular and intrathoracic LN	2 NRTI	2	30	110	NS	↓0.9 log	NS
	No	Cervical LN	2 NRTI + PI	2	10	210	NS	↓2.8 log	NS
	No	Supraclavicular LN	2 NRTI + PI	4	30	40	NS	↓2.9 log	NS
	No	Inguinal LN	2 NRTI	7	30	260	NS	NS	NS
	No	Intra-abdominal LN	2 NRTI + PI	3	90	NS	NS	NS	NS
	No	Cervical LN	2 NRTI + PI	1	20	110	NS	↑0.2 log	NS
Foudraire ⁵⁵	No	Hepatosplenomegaly; intrathoracic and cervical LN	2 NRTI + PI	1-5	10	160	>9 000 000	1 000 000	ART interrupted
	No	Intra-abdominal LN	2 NRTI	4	40	200	>1 000 000	120 000	Nil
	No	Intrathoracic LN	2 NRTI + PI	12	20	100	>1 000 000	120 000	Nil
	No	Intrathoracic LN, pulmonary	2 NRTI + PI	1	<10	<10	>100 000	<1000	Nil
Behrens ⁵³	No	Intrathoracic LN, endobronchial lesion	2 NRTI + PI	8	9	54	280 000	<LLD	Nil
Price ⁵⁴	No	Cervical, axillary, intrathoracic LN	2 NRTI + PI	8	14	180	376 000	890	Nil

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and their cell wall components persist in host tissues for weeks after initiation of antimycobacterial treatment is probably an important factor contributing to the high frequency of IRD developing in association with this particular group of organisms.

Some cases of IRD develop within the first 1–2 weeks of HAART, even before any detectable increase in circulating CD4 cell numbers, reflecting the rapid improvements in immune function that result from the precipitous decline in HIV load.^{39,40} T-lymphocyte proliferative responses to mycobacterial antigens are restored^{26,38,42–44} and development of MAC-associated IRD is paralleled by increases in T-lymphocyte proliferative responses to mycobacterial antigens detectable as early as 2 weeks after starting treatment.²⁶ A general switch from type 2 to type 1 cytokine profiles in T-lymphocyte stimulation assays is also detectable early in treatment, with increases in interferon γ and interleukin 2 production.⁴⁵ Interferon γ secretion and cell-mediated immune responses to mycobacteria are restored,⁴³ leading to restoration of DTH skin test responses to mycobacterial antigens.^{27,46}

The ability of the host to form granulomas is re-established during HAART. An unusually vigorous granulomatous response with or without caseation is described with MAC-associated IRD.^{47–50} Lymph nodes involved in mycobacterial IRD may show clinical suppuration, and biopsy specimens of affected tissues may reveal a degree of necrotising inflammation that is unusual in the context of profoundly immunocompromised patients.^{27,51–55} Reports of hypercalcaemia during mycobacterial IRD provide further indirect evidence that HAART restores the ability to form physiologically functioning granulomas.^{13,56} Hypercalcaemia is a well-recognised complication of mycobacterial infection, arising as a result of production of 1,25-dihydroxycholecalciferol in functional granulomas.⁵⁷ Elevated serum concentrations of 1,25-dihydroxycholecalciferol and hypercalcaemia during mycobacterial IRD reflect restoration of the ability of the host to form physiologically functioning granulomas.

Thus, HAART reverses the impact of HIV on the host granulomatous response to mycobacteria. However, the

(continued) Reference	Previous MAC	Manifestation	ART regimen	Weeks on ART	CD4 count × 10 ⁶ /L		VL copies/mL		Adjunctive interventions
					Baseline	IRD	Baseline	IRD	
Thaker ⁶⁴	No	Intrathoracic LN	2 NRTI + PI	8	63	250	750 000	1850	Nil
French ²⁸	No	Localised LN	HAART	1	42	78	NS	NS	Nil
	Yes	Localised LN	HAART	1	12	57	NS	NS	Steroids
	No	Localised LN	HAART	6	9	12	NS	NS	Steroids
	No	Localised LN	HAART	4	91	182	NS	NS	Nil
	No	Hepatomegaly	HAART	1	42	231	NS	NS	Nil
Brown ⁶⁵	Yes	Skin lesions, leukaemoid reaction	2 NRTI, NNRTI	7	10	70	202 300	10 700	Steroids
Hassell ⁶⁶	No	Axillary LN	2 NRTI	2	1015	960	294 785	99	Steroids
Aberg ⁶⁷	No	Spinal osteomyelitis, paraparesis	NNRTI + 2PI	>52	16	465	NS	<LLD	Surgery
	No	Spinal osteomyelitis, paraparesis	NRTI + 2PI	>52	23	118	NS	<LLD	Surgery
Zamir ⁶⁹	No	Choroiditis	2 NRTI + PI	8	20	37	385 000	<LLD	Eucleation of eye
Shelburne ¹³	Yes	Intra-abdominal LN	2 NRTI + PI	1.5	30	140	NS	NS	Nil
	Yes	Hepatosplenomegaly, intra-abdominal LN, hypercalcaemia	2 NRTI + PI	3	30	170	424 476	<LLD	Nil
	NS	Colitis	HAART	5	23	44	102 200	42 420	NS
de Boer ⁶⁸	No	Intrathoracic LN	2 NRTI + PI	16	4	71	267 000	<LLD	Nil
	NS	Extrapulmonary (unspecified)	2 NRTI + PI	3	2	50	NS	NS	NS
	NS	NS	2 NRTI + 2PI	5	10	180	NS	NS	NS
	NS	NS	2 NRTI + PI	7	40	90	NS	NS	NS
	NS	Extrapulmonary (unspecified)	2 NRTI + 2PI	8	43	533	NS	NS	NS
	NS	NS	2 NRTI + PI	21	43	54	NS	NS	NS
Salama ⁶⁹	No	Intrathoracic LN, endobronchial mass	2 NRTI + PI	2	4	20	NS	NS	Nil
	No	Intrathoracic LN, endobronchial mass, pulmonary	2 NRTI + PI	8	45	145	252 000	<LLD	Nil
	No	Intrathoracic LN, pulmonary	2 NRTI + PI	>4	38	142	750 000	<LLD	Nil
Buckingham ⁷⁰	Yes	Intrathoracic LN and tracheal compression	2NRTI + NNRTI	28	AD	AD	AD	AD	Steroids
	No	Intrathoracic LN and pulmonary	2NRTI + NNRTI	2.5	AD	AD	AD	AD	Nil
Lawn ⁶⁸	No	Pyomyositis, cutaneous abscesses	2 NRTI + NNRTI	2	84	110	>500 000	1000	Surgery

AD=aggregate data; ART=antiretroviral treatment; HAART=highly active antiretroviral therapy; IRD=immune reconstitution disease; <LLD=viral load is less than the lower limit of detection; LN=lymphadenopathy; MAC=Mycobacterium avium complex; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NS=not stated; PI=protease inhibitor; VL=plasma viral load.

Table 1: Reported cases (n=64) of immune reconstitution disease associated with Mycobacterium avium complex

rapidity with which this occurs and perhaps a lack of compensating immunoregulatory mechanisms may lead to the uncontrolled tissue-damaging responses that characterise IRD. There is some speculation that some patients may have a genetically determined immunological predisposition to development of IRD.⁵⁸ Polymorphisms in cytokine genes may influence the rate of clearance of opportunistic pathogens or may cause dysregulation of the inflammatory response. The association of such polymorphisms with the development of IRD has been described in groups of patients developing IRD associated with a range of organisms.⁵⁸ However, whether mechanistic relations exist has yet to be elucidated.

IRD and Mycobacterium avium complex

MAC typically causes disease in patients with AIDS and end-stage immunodeficiency. Usually, the organism can be cultured from a disseminated infection in the blood or bone marrow; focal organ disease is infrequent. The first reports of IRD associated with HAART were among HIV-infected patients presenting with unusual clinical manifestations of MAC infection, such as localised lymphadenitis or endobronchial mass lesions (table 1). Biopsy samples showed an unusual degree of inflammation and evidence of granuloma formation and

caseation. MAC could be cultured from affected tissues but not from blood. The phenomenon was first clearly characterised in 1992 among patients receiving zidovudine monotherapy and was associated with restoration of DTH responses to mycobacterial antigens.²⁷ However, on careful review of the literature, other cases of unusual localised MAC infection were reported as early as 1988 among patients who had recently started zidovudine treatment.^{55,59} The authors of these papers speculated, probably correctly, that these unusual presentations were attributable to the improved immune function due to zidovudine.

Since the advent of HAART in the mid-1990s, many reports of MAC-associated IRD have been published. We have identified 25 papers describing 64 cases (table 1). The majority of cases developed in patients with no preceding history of MAC infection. Manifestations of IRD developed after a median of 4 weeks (IQR 2–8 weeks; range 1–52 weeks) of HAART. Patients had a nadir blood CD4 lymphocyte count of 25 cells/ μ L (IQR 10–39 cells/ μ L) before starting HAART and a median plasma viral load of 3×10^5 RNA copies/mL (range 1×10^3 – 9×10^6 copies/mL). At the time IRD was diagnosed the blood CD4 lymphocyte count had increased to a median of 140 cells/ μ L (IQR 69–180 cells/ μ L) and the plasma viral load had decreased to below the lower limit of

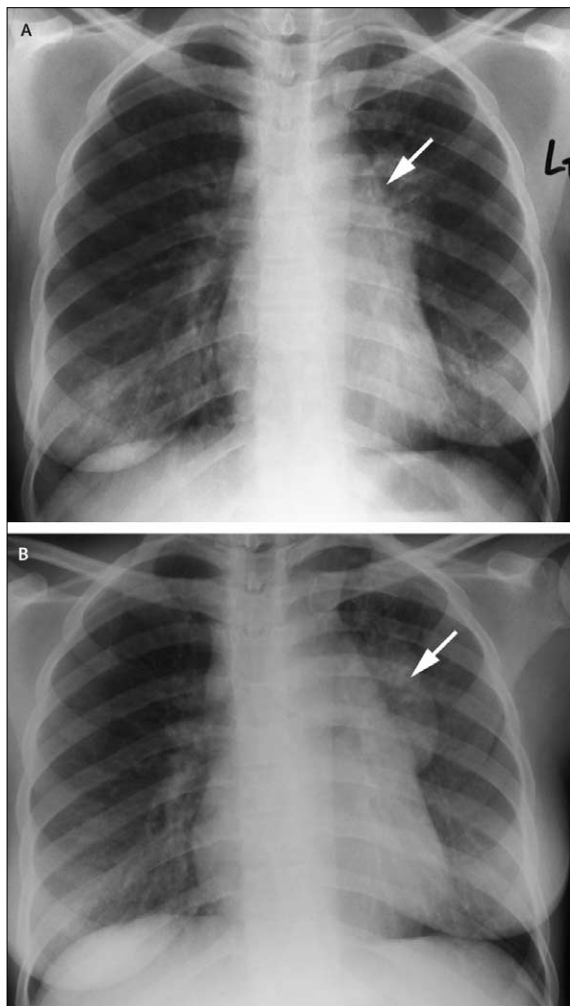


Figure 1: (A) Chest radiograph of an HIV-infected patient at the time of starting HAART showing minor left hilar and aortopulmonary lymphadenopathy (arrow). (B) 17 days after starting HAART, massive mediastinal lymphadenopathy (arrow) and a nodular infiltrate in the mid and lower zone developed due to IRD associated with *M avium* infection. Reproduced from reference 70 with permission from W B Saunders.

detection in over half the patients. Thus, MAC-associated IRD typically develops in profoundly immunosuppressed individuals who have an excellent response to HAART.

MAC-associated IRD most commonly presents with fever and lymphadenopathy or lymphadenitis, which is often painful and may suppurate. Among reviewed cases (table 1), lymphadenopathy was present in 44 cases (69%). Lymphadenopathy was peripheral (cervical, supraclavicular, axillary, or inguinal) in 22 cases, most commonly affecting a single lymph node group; intrathoracic nodes were involved in 19 patients (figure 1) and intra-abdominal nodes in nine patients. Development of paratracheal lymphadenopathy has been reported to cause upper airway compression.⁷⁰ Pulmonary disease was the second most common manifestation (n=12; 19%) with patients developing

respiratory symptoms associated with lung parenchymal changes on chest radiographs (n=7) or discrete endobronchial lesions causing partial or complete airway obstruction (n=7).

Several reports describe MAC-associated IRD affecting the musculoskeletal system, including septic arthritis and adjacent osteomyelitis,⁶⁰ spinal osteomyelitis with paraparesis,⁶⁷ psoas abscesses,⁶² and pyomyositis of the lower limb (figure 2).⁴⁸ Skin lesions are described in four patients, including nodules and subcutaneous abscesses.^{27,47,48,65} Hepatosplenomegaly,^{13,26} lesions of the small and large intestine,¹³ iritis leading to visual loss,⁴⁹ a leukaemoid reaction in peripheral blood,⁶⁵ and hypercalcaemia¹³ are also reported.

All patients received specific antimycobacterial treatment for MAC infections and lesions almost invariably responded well to treatment, as might be expected in the context of an organism of low virulence and a vigorous host inflammatory response. HAART was interrupted in only three patients. Suppurating lymph nodes in six patients were surgically drained and psoas abscesses in two patients were drained under radiological guidance. Surgical intervention was also required in several patients to treat endobronchial disease, spinal disease, pyomyositis, cerebral disease, ocular disease, and septic arthritis. Corticosteroids were prescribed in addition to antimycobacterial drugs in only four patients.

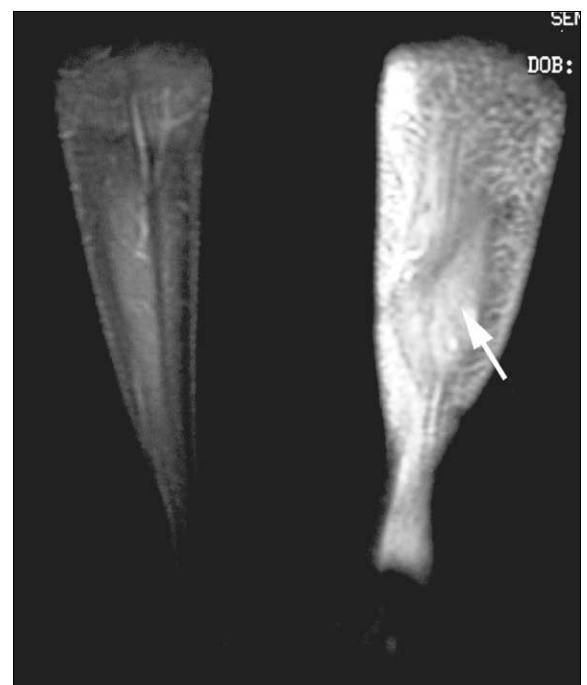


Figure 2: Coronal T1-weighted magnetic resonance images without contrast through the right and left lower legs of an HIV-infected patient 2 weeks after starting HAART

This shows IRD associated with *M avium* complex presenting as pyomyositis (arrow), which is associated extensive soft tissue inflammation within the left gastrocnemius muscle. Reproduced from reference 48 with permission from University of Chicago Press.

Reference	n	Site of TB pre-ART	Manifestation	Duration (weeks)*		ART regimen	CD4 count × 10 ⁶ /L*		VL copies/mL*		Adjunctive interventions
				TB treatment	ART		Baseline	IRD	Baseline	IRD	
Narita ¹⁸	12	NS	Intrathoracic LN (6), cervical LN (5), alveolitis (4), pleural effusion (2) ascites (1), cutaneous (1)	11 (4-5-31)	2 (0.5-4.5)	3 NRTI or 2 NRTI + PI	54 (2-133)	66 (5-283)	750 000 (31 987-4 275 175)	4274 (<LLD - 6527)	ART interrupted (1)
Crump ⁷¹	1	None	Cervical LN, miliary, intracranial tuberculoma	20	24	2 NRTI + PI	210	NS	325 000	<LLD	Steroids
John ⁷²	1	Pulmonary, intrathoracic LN	Intrathoracic LN and alveolitis	20	12	2 NRTI + PI	55	320	900 801	<LLD	Oxpentifylline
Chien ⁷³	1	Pulmonary	Intrathoracic and cervical LN	6	6	2 NRTI	220	420	>750 000	NS	Steroids
Kunimoto ⁷⁴	1	Pulmonary	Pulmonary alveolitis	8	1	2 NRTI + PI	9	NS	17 000	NS	Steroids
Furrer ⁷⁵	3	Liver and intestine	Hepatosplenomegaly, intra-abdominal LN	6	<2	2 NRTI + PI	25	NS	750 000	NS	Steroids
		Pulmonary and peritoneal	Pleural effusion, ascites and hepatosplenomegaly	18	<2	2 NRTI + PI	37	NS	74 000	NS	Steroids
		Pulmonary and urogenital	Epididymo-orchitis	8	<2	2 NRTI + PI	26	NS	290 000	NS	Steroids
French ²⁸	1	Pulmonary, intrathoracic LN	Intrathoracic LN and alveolitis	NS	10	HAART	55	320	NS	NS	NS
Fishman ¹⁷	7	Pulmonary	Parenchymal (5), effusion (3) Intrathoracic LN (5), cervical LN (2) Ascites (1), cutaneous (1)	NS	2 (1-4.5)	HAART	47 ± 33	AD	NS	NS	NS
Orlovic ⁷⁶	1	Miliary	Increased cervical LN	5	5	2 NRTI + PI	103	178	1006	NS	Nil
Wendel ⁷⁷	3	NS	Psoas abscess (2) Unspecified LN (3)	NS	<4	2 NRTI + PI	69	NS	NS	NS	Surgery (3)
Navas ⁷⁸	6	NS	Pulmonary (2), LN (4)	NS	NS	2 NRTI + PI	46.5 (30-312)	↑71 (12-220)	6.1 log (6.0-6.3)	↓2.4 log (2.1-4.2)	ART interrupted (4) Steroids (2)
Bottiau ⁷⁹	1	Disseminated	Subhepatic abscess, generalised and intra-abdominal LN pleural effusions, ascites	3	5	2 NRTI + PI	19	NS	750 000	NS	ART interrupted + steroids
Shelburne ¹³	1	Pulmonary	Intra-abdominal LN	2	1	2NRTI + PI	30	90	468 907	<LLD	Steroids
	1	None	Presentation of caecal TB	0	24	2 NRTI + NNRTI	177	234	17 700	<LLD	Surgery
Wanchu ⁸⁰	1	Mediastinal	Cervical LN, intra-abdominal LN	12	2	2NRTI + PI	26	NS	48 500	NS	Nil
Guex ⁸¹	1	Ileocaecal	Ileocaecal perforation	48	44	2 NRTI + PI	29	167	111 400	<LLD	Surgery
Fernandes ⁸²	1	Cervical LN	Cervical LN	8	8	2 NRTI + NNRTI	177	328	230 000	44 000	Steroids
	1	Pulmonary	Mediastinal, cervical, inguinal LN	8	2	NRTI + NNRTI	187	264	93 618	<LLD	Thalidomide, steroids
	1	Pulmonary	Cervical LN	NS	24	2 NRTI + NNRTI	38	62	43 000	20 000	Nil
Goldsack ⁸³	1	None	Respiratory failure	NS	2	2 NRTI + NNRTI	121	298	413 000	23 000	Ventilation
Ramos ⁸⁴	1	Disseminated	Cervical LN, miliary	2	2	3 NRTI	68	NS	758 000	NS	Steroids
Vidal ⁸⁵	1	Brain abscess	Expansion brain abscess	8	4	HAART	55	110	160 000	<LLD	Steroids
de Lange ⁸⁶	1	Intrathoracic LN	Axillary, pulmonary, intra-abdominal abscesses	NS	2.5	2NRTI + PI	10	200	969 000	1000	Nil
De Boer ⁸⁸	1	NS	Extrapulmonary (unspecified)	NS	17	2 NRTI + PI	110	210	NS	NS	NS
	1	NS	Extrapulmonary (unspecified)	NS	25	2 NRTI + PI	30	360	NS	NS	NS
	1	NS	Extrapulmonary (unspecified)	NS	31	2 NRTI, 2PI	21	518	NS	NS	NS
Buckingham ⁷⁰	1	PTB, LN	Tracheal compression by LN	9.5	8	2NRTI + NNRTI	AD	AD	AD	AD	NS
	1	PTB, LN	Alveolitis, pleural effusion	9.5	1.5	2NRTI + NNRTI	AD	AD	AD	AD	NS
Breen ⁷⁹	14	Disseminated (9)	Alveolitis (2), LN (7) pleural effusion (1), ascites (1), CNS (unspecified) (2)	5 (0.5-25)	1.5 (1-2.5)	Dual or triple	AD	AD	AD	AD	NS
Lawn ⁵⁶	1	PTB	Alveolitis and hypercalcaemia	12	4	NNRTI+ 2PI	8	110	456 778	451	Steroids
Jehle ⁸⁷	1	Miliary	Acute renal failure	8	6	2 NRTI + PI	68	82	1 247 786	104	Steroids
Breton ⁸⁸	16	Disseminated	LN (11), splenic abscess (3) intestinal (3), pulmonary (2), skin (1), parotitis (1)	NS	NS	HAART (14) 2 NRTI (2)	75 (4-435)	NS	270 000 (60 000-1 600 000)	NS	Steroids (6) ART interrupted (7) Surgery (1)

*Median (range). AD=aggregate data; ART=antiretroviral treatment; CNS=central nervous system; HAART=highly active antiretroviral therapy; IRD=immune reconstitution disease; <LLD=viral load is less than the lower limit of detection; LN=lymphadenopathy; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NS=not stated; PI=protease inhibitor; PTB=pulmonary tuberculosis; TB=tuberculosis; VL=plasma viral load.

Table 2: Reported cases (n=70) of immune reconstitution disease associated with *Mycobacterium tuberculosis*

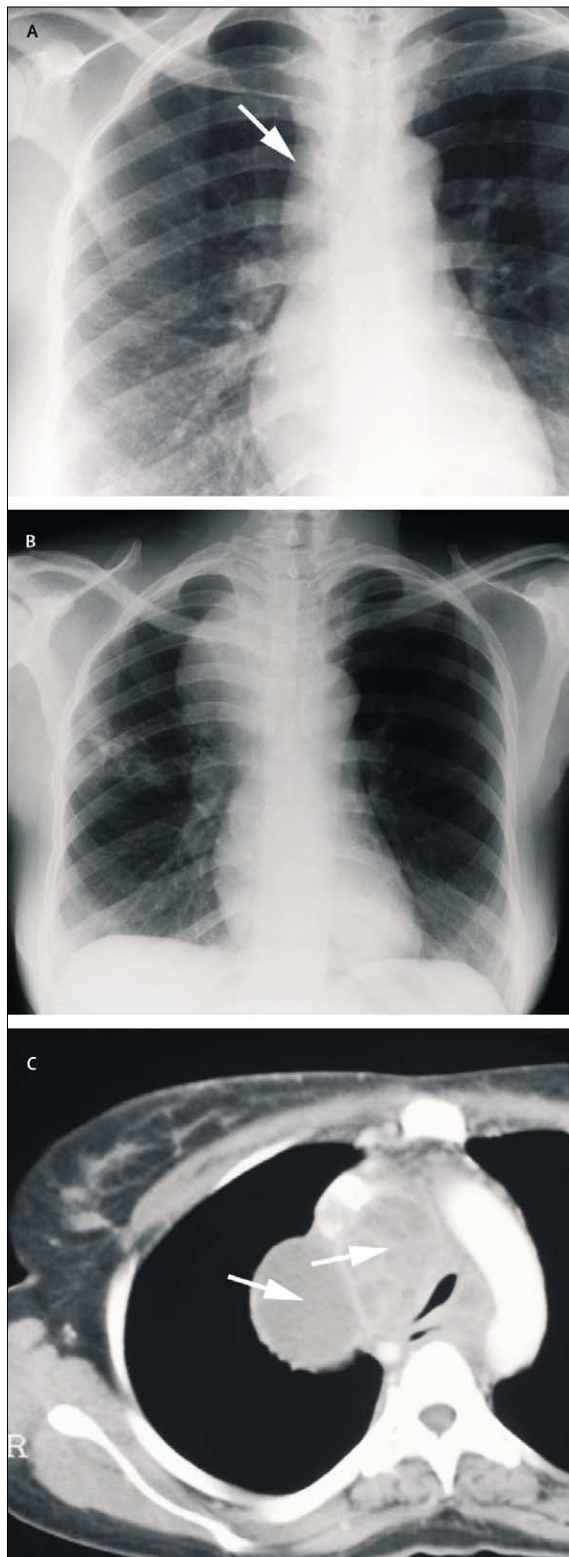
No fatalities attributable to MAC IRD have been described.

IRD and *M tuberculosis*

By contrast with MAC, IRD associated with *M tuberculosis* was not reported among individuals receiving zidovudine

monotherapy. The first reports of *M tuberculosis*-associated IRD were in 1998 after the advent of HAART (table 2). Because paradoxical reactions to antituberculosis treatment have long been recognised, clinical deterioration attributable to zidovudine-mediated IRD may have simply been ascribed to a “normal” paradoxical

reaction. Clinically apparent paradoxical reactions are reported to occur among 29–36% of tuberculosis/HIV co-infected patients receiving both antituberculosis



treatment and newly commenced HAART;^{18,19,78} radiological deterioration is reported among 46% of such patients.¹⁷ Although the majority of these studies are limited by retrospective design, a prospective study by Narita and colleagues¹⁸ identified paradoxical reactions among 12 of 33 (36%) co-infected patients receiving both tuberculosis treatment and HAART, compared with only two of 28 (7%) co-infected patients receiving tuberculosis treatment alone. A finding common to several studies is that the risk of paradoxical reactions is strongly associated with starting HAART within the first 2 months of tuberculosis treatment.^{18,19,78} Other factors associated with IRD include extrapulmonary and disseminated tuberculosis, a lower CD4 lymphocyte count and higher viral load before starting HAART, and a greater reduction in viral load and greater CD4 increment during HAART.^{18,88}

We identified 27 papers describing 86 cases of *M tuberculosis*-associated IRD (table 2). By contrast with MAC-associated IRD, the great majority of cases developed in patients with a diagnosis of tuberculosis that antedated the commencement of HAART; only rarely was IRD the first presentation of tuberculosis.^{13,83} In most patients, HAART was started during the first 2 months of antituberculosis treatment. The median duration of antituberculosis treatment before the onset of IRD was 8 weeks (IQR 5.5–11.5 weeks; range 2–48 weeks) whereas the median duration of HAART was only 4 weeks (IQR 2–10 weeks; range 1–44 weeks). Patients had a nadir blood CD4 lymphocyte count of 51 cells/ μ L (IQR 26–103 cells/ μ L; range 8–220 cells/ μ L) before starting HAART and a median plasma viral load of 3.7×10^5 RNA copies/mL (range 1×10^3 – 1×10^7 copies/mL). At the time IRD was diagnosed the blood CD4 lymphocyte count had increased to a median of 205 cells/ μ L (IQR 110–298 cells/ μ L) and the plasma viral load had dramatically decreased, reaching the lower limit of detection in approximately half the patients.

The most commonly reported manifestations of *M tuberculosis*-associated IRD were fever, lymphadenopathy, and worsening respiratory symptoms. In common with MAC, lymphadenopathy was the most frequent manifestation, occurring in 61 (71%) of the patients (table 2). Lymphadenopathy with or without overt lymphadenitis was most frequently peripheral (cervical, supraclavicular, axillary, or inguinal), but overt suppuration was uncommonly reported. Intrathoracic lymphadenopathy was described in about one-fifth of

Figure 3: (A) Chest radiograph of an HIV-infected patient showing right paratracheal lymphadenopathy (arrow) and a reticulonodular infiltrate due to *Mycobacterium tuberculosis* infection. (B) After 2 months of antituberculosis therapy and HAART, the patient presented with stridor. A repeat chest radiograph shows massive right paratracheal adenopathy displacing and compressing the trachea, minor right hilar adenopathy, and a nodular infiltrate in the mid-zone. (C) Computed tomography shows a 6×7 cm nodal mass in the right paratracheal region (arrow) causing displacement and compression of the trachea

Reproduced from reference 70 with permission from W B Saunders.

Reference	IRD manifestation	New presentation or deterioration	ART regimen	Weeks on ART	CD4 count × 10 ⁶ /L		VL copies/mL		Adjunctive interventions
					Baseline	IRD	Baseline	IRD	
<i>Mycobacterium xenopi</i>									
Foudraire ⁶⁵	Pulmonary and pleural effusion	Presentation	2 NRTI + PI	4	19	>200	1 000 000	1000	Nil
Bachmeyer ⁶⁹	Cavitating pulmonary	Presentation	2 NRTI + NNRTI	8	48	225	150 229	114	Nil
De Boer ⁶⁸	Extrapulmonary (unspecified)	NS	2NRTI, NNRTI, 2PI	12	19	105	NS	NS	NS
Buckingham ⁷⁰	Pulmonary	Deterioration	2NRTI + NNRTI	3	AD	AD	AD	AD	Nil
<i>Mycobacterium genavense</i>									
Phillips ⁵¹	Cervical LN	Presentation	2 NRTI	1	60	170	NS	↓2.4 log	NS
<i>Mycobacterium scrofulaceum</i>									
Lawn ⁹⁰	Bilateral parotitis and cervical LN	Presentation	2 NRTI + NNRTI	8	6	80	420 000	<50	Nil
<i>Mycobacterium kansasii</i>									
Naccache ⁶¹	Pulmonary	Presentation	2 NRTI + PI	1	71	214	500 000	10 000	Nil
Lawn ⁹²	Pulmonary and respiratory failure	Deterioration	2 NRTI + PI	3	340 (11%)	348	260 000	925	Steroids
<i>Mycobacterium leprae</i>									
Lawn ⁹³	Leprosy and reversal reaction	Presentation	2 NRTI + NNRTI	4	10	70	120 000	1000	Steroids
Pignataro ⁶⁴	Leprosy and reversal reaction	Presentation	2 NRTI + PI	8	147	499	NS	NS	NS
	Leprosy and reversal reaction	Deterioration	2 NRTI + NNRTI	4	37	200	NS	NS	NS
Couppie ⁶⁵	Leprosy and reversal reaction	Presentation	3 NRTI	6	87	257	19 000	<650	Nil
	Leprosy and reversal reaction	Presentation	3 NRTI	8	130	278	40 701	68	Steroids
	Leprosy and neuritis	Presentation	2 NRTI + PI	12	31	171	62 700	50	Steroids
BCG									
Sharp ⁶⁶	Axillary and supraclavicular LN	Presentation	2 NRTI	2	10%	26%	4 400 000	77 000	Nil
Hesseling ⁹⁷	Axillary LN	Presentation	HAART	4	10%	NS	43 000	NS	NS

AD=aggregate data; ART=antiretroviral treatment; HAART=highly active antiretroviral therapy; IRD=immune reconstitution disease; LN=lymphadenopathy; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NS=not stated; PI=protease inhibitor; VL=plasma viral load

Table 3: Reported cases (n=16) of immune reconstitution disease associated with other non-tuberculous mycobacteria and BCG

patients and two reports describe tracheal compression by intrathoracic nodes (figure 3).^{70,88}

The second most common manifestation was the development or deterioration of parenchymal lung disease as seen in 24 (28%) patients (table 2), occasionally leading to respiratory failure.^{74,83} However, unlike MAC-associated IRD, endobronchial lesions have not been reported, but pleural effusions (n=9) and ascites (n=5) are described. Other miscellaneous manifestations include hepatosplenomegaly,^{19,71,85} psoas abscess,⁷⁷ splenic abscess,⁸⁸ other intra-abdominal abscesses,⁷⁹ disease of the caecum with or without perforation,^{13,81} epididymo-orchitis,⁷⁵ central nervous system lesions,^{19,71,85} skin lesions,^{17,18,88} ureteric compression,⁸⁸ acute renal failure,⁸⁷ and hypercalcaemia.⁵⁶

Although some manifestations of *M tuberculosis*-associated IRD were life-threatening, including acute respiratory failure,^{74,83} airway obstruction,^{70,88} peritonitis due to bowel perforation,⁸¹ splenic rupture,⁸⁸ and expanding intracranial lesions,⁷¹ no deaths have been reported. All patients received antituberculosis therapy; HAART was interrupted in 13 (15%) patients and six (7%) required surgery. Immune-modulating treatments were more frequently prescribed than for patients with MAC-associated IRD, often with rapid effect. Corticosteroids were received by 22 (26%) patients and thalidomide and pentoxifylline were each received by one patient (table 2).

IRD and other mycobacteria

IRD associated with other non-tuberculous mycobacteria and BCG are infrequent and are described among only

16 patients (table 3), comprising 10% of all cases reviewed. Isolation of *M xenopi* from sputum is uncommonly associated with disease and the need for routine treatment of this organism in HIV-infected individuals receiving HAART is doubtful.⁹⁸ However, this organism has been implicated in IRD with pulmonary



Figure 4: Leprosy presenting as immune reconstitution disease after 4 weeks of HAART

The photograph shows the cutaneous lesions of borderline tuberculoid leprosy with reversal reaction and thickening of the greater auricular nerve (arrow). Reproduced from reference 93 with permission from University of Chicago Press.

Panel 2: Summary points

Mycobacteria are the pathogens most commonly associated with IRD, comprising approximately 40% of cases reported in the literature up to 2002.

IRD associated with mycobacteria typically presents in patients with profound immunodeficiency (median CD4 count <50 cells/ μ L) after a median of 4 weeks HAART. The clinical manifestations of IRD associated with mycobacteria are extremely diverse, potentially affecting any organ in the body.

MAC-associated IRD most commonly manifests with new onset fever and localised lymphadenopathy (approximately 70%) or respiratory disease (about 20%).

M tuberculosis-associated IRD most commonly presents with fever and the clinical deterioration of pre-existing lymphadenopathy (about 70%) or respiratory disease (approximately 30%).

Commencement of HAART during the first 2 months of antituberculosis treatment is a strong risk factor for IRD. However, this may be necessary in those with AIDS because of the risk of further opportunistic infections.

Patients with AIDS should be carefully screened for mycobacterial infections before commencing HAART.

IRD may emerge as an important problem in developing countries where access to HAART is being expanded and the burden of mycobacterial disease is very high.

The need to discontinue HAART during IRD is unusual, but is recommended with life-threatening disease.

A minority of patients require adjunctive oral corticosteroids to control IRD, usually with rapid effect.

disease in four patients, including the development of cavitation and a pleural effusion (table 3). All presented in the first 3 months of HAART among patients with a pretreatment CD4 lymphocyte count of less than 50 cells/ μ L and all resolved without complication.²⁶ Respiratory failure due to IRD associated with *M kansasii* has also been reported.⁹²

Administration of BCG to HIV-infected infants is known to be associated with an increased risk of disseminated BCG infection or "BCGosis".⁹⁹ However, two publications report BCG-associated IRD, manifesting as axillary and supraclavicular lymphadenitis (table 3). These two children, who received BCG at birth, started HAART at 3 and 8 months of age. Both developed BCG lymphadenitis in the first month of HAART and required antimycobacterial treatment. These reports are the only occurrences of mycobacterial IRD among children that we found.

Search strategy and selection criteria

Multiple Medline searches of literature published in English were done using the following terms: "immune restoration", "immune reconstitution", "immune restitution", "immunorestitution", "immune reconstitution inflammatory syndrome", "IRIS", "paradox*", "HIV", "AIDS", "mycobacter*", "tuberculosis", "leprosy", "BCG" and "Bacille Calmette-Guerin". Searches were complete up to the end of February 2005. Many additional references were identified from citations in other published papers.

The advent of the AIDS pandemic initially awoke fears that leprosy control would deteriorate, as has been the case with tuberculosis. However, HIV-1 infection has little impact on risk of development of leprosy or the clinicopathological features of the disease.¹⁰⁰ This lack of impact has remained an enigma. However, over the past 2 years, the presentation of leprosy as IRD has been reported among six cases (table 3). In five patients, IRD was the first presentation of leprosy, and in one patient IRD presented as the clinical deterioration of a pre-existing skin lesion. All were borderline forms of leprosy with reversal reaction (figure 4), developing within 3 months of starting HAART (median 7 weeks, range 4–12 weeks). The pre-HAART median CD4 lymphocyte count was 62 cells/ μ L (range 10–147 cells/ μ L). Leprosy presenting as IRD is likely to be seen increasingly frequently as antiretroviral therapy becomes more widely available among the communities in India, Africa, and South America where leprosy is endemic.

Prevention and treatment of IRD

From the cases reviewed, it is clear that the vast majority of cases of IRD develop in patients with a nadir CD4 lymphocyte count of less than 100 cells/ μ L (median <50 cells/ μ L), a viral load of more than 10^5 copies/mL, and with a rapid response to combination antiretroviral treatment. This finding is to be expected since advanced immunodeficiency is associated with increased likelihood of subclinical mycobacterial infections, high mycobacterial antigen load, increased likelihood of disseminated infection, and greater potential for major rapid increases in immune function during HAART. Such patients require careful screening for subclinical infection before starting HAART by careful clinical review, routine blood analyses, chest radiology, examination of induced sputum specimens, and culture of blood for mycobacteria.

The over-riding risk factor for tuberculosis-associated IRD is starting HAART within the first 2 months of antituberculosis treatment when a substantial mycobacterial antigen load may still be present in diseased tissues. Such timing leads to synchronisation of paradoxical reactions associated with antituberculosis treatment and IRD associated with HAART, effectively maximising the risk of clinical deterioration. The high frequency of such reactions has led some researchers to recommend that HAART should be delayed until 2 months after antituberculosis treatment has been started.¹⁰¹ However, retrospective studies in London concluded that although commencement of HAART in patients with tuberculosis and CD4 lymphocyte counts greater than 100 cells/ μ L might be deferred, those with CD4 lymphocyte counts less than 100 cells/ μ L have a high risk of morbidity and mortality associated with new opportunistic infections and might best be treated earlier.^{102,103} Further research is needed, including studies based in countries with high rates of tuberculosis/HIV co-

infection. Of note, it seems that the mortality rate of patients with end-stage AIDS is much higher in low income countries compared with industrialised countries.¹⁰⁴ Deferment of HAART in patients with tuberculosis in low income countries is likely to be accompanied by an unacceptable mortality rate. The contribution of IRD to mortality, though, has not been quantified in such settings.

Reports of adjunctive drug treatment of mycobacterial IRD are anecdotal and clinical trials of treatment are lacking. Formal studies of treatment are difficult for several reasons: IRD is a sporadic phenomenon, there is no clear-cut case definition, and most cases will resolve without any additional treatment other than antimycobacterial drugs. In the majority of cases, HAART can be safely continued without need for interruption. However, our own experience and that reported in the literature is that patients who are compromised—eg, by worsening respiratory function—respond very quickly to a course of oral corticosteroids that can be tapered according to response. The dose and duration required is very variable and should be judged clinically. Furthermore, the induction of steroid metabolism by rifampicin should be taken into account. Severe disease will require at least 1–2 mg/kg of prednisolone. A randomised, placebo-controlled trial of prednisolone in the management of tuberculosis-associated IRD is currently underway in Cape Town, South Africa with efficacy and toxicity both being end-points. In cases where IRD is life-threatening, HAART should be temporarily discontinued until the clinical condition has improved and the underlying infection treated.

IRD in developing countries

HAART is now becoming more widely accessible in developing countries where HIV is associated with a different spectrum of opportunistic infections, often with a very high incidence of tuberculosis.¹⁰⁵ Newly established community-based antiretroviral projects in developing countries are being accessed by increasing numbers of adults and children with advanced symptomatic disease and profound CD4 lymphocytopenia. Our experience in Cape Town is that *M tuberculosis*-associated IRD is emerging as a substantial problem. At an antiretroviral programme based in a township where local rates of tuberculosis are 1400/100 000 per year and the antenatal HIV prevalence is almost 30%, there is a major overlap of tuberculosis with HAART. Approximately 10% of patients are receiving tuberculosis treatment when they are referred for HAART and another 5% are found to have tuberculosis on pre-HAART screening. Furthermore, another 10% of these patients develop tuberculosis during the first year of HAART. Our impression is that IRD does contribute substantially to the burden of disease among these patients during HAART, but this as yet remains unquantified. Clearly more research is needed. In such settings where tuberculosis and HIV are so prevalent, it

may be possible to gain much more information about this intriguing phenomenon of IRD, including its prevention and management (panel 2).

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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