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Immune Restoration Diseases Reflect Diverse Immunopathological Mechanisms

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INTRODUCTION

Up to one in four patients infected with human immunodeficiency virus type 1 (HIV-1) and given antiretroviral therapy (ART) experience inflammatory or cellular proliferative disease associated with a preexisting opportunistic infection. Many such infections are subclinical or quiescent before the patient begins ART. Symptomatic disease is most common in patients starting treatment with low CD4 T-cell counts and is attributed to poor regulation of the restored immune system. The conditions were originally referred to as immune restoration diseases (IRD) to differentiate them from immunodeficiency diseases (50, 51), but immune reconstitution inflammatory syndrome (IRIS) is also used. The terms should be considered synonymous. The genetic associations of IRD differ with the causative agent (113, 114), so we consider the clinical diversity in IRD to reflect diverse immunopathological mechanisms. IRD associated with intracellular pathogens were originally characterized by delayed-type hypersensitivity (DTH) immune responses, demonstrated by skin testing with mycobacterial antigens (50, 51, 86), and/or by granulomatous inflammation in tissues affected by IRD associated with mycobacteria (108), cryptococci (84), *Histoplasma* sp. (14), and *Leishmania* sp. (110). Mycobacterial and cryptococcal IRD have been attributed to a pathological overproduction of Th1 cytokines, particularly gamma interferon (IFN-γ) (9, 138).

Clinicopathological and immunological characteristics of IRD associated with viral infections suggest that pathogenic mechanisms are different. For example, IRD associated with varicella-zoster virus (VZV) or JC polyomavirus infection correlates with a CD8 T-cell response in the central nervous system (CNS) (29, 98). Exacerbations or de novo presentations of hepatitis associated with hepatitis C virus (HCV) infection following ART may also reflect restoration of pathogen-specific immune responses as titers of antibodies to HCV core antigen rise in parallel with the alanine transaminase (ALT) level and with levels of soluble CD26 (sCD26) and sLAG-3, which are plasma markers of T-cell activation (135; P. Price, unpublished data).

Until recently, immunological studies have been limited by the availability of longitudinal sample sets that include peripheral blood mononuclear cells (PBMC), plasmas, and/or tissues collected before and during IRD. Each archive must include samples from patients with similar preexisting infections and immune statuses but with an uneventful immune recovery. Correlations between these immunological parameters and clinical presentations will make it possible to tease out distinct immunological scenarios described collectively as IRD.

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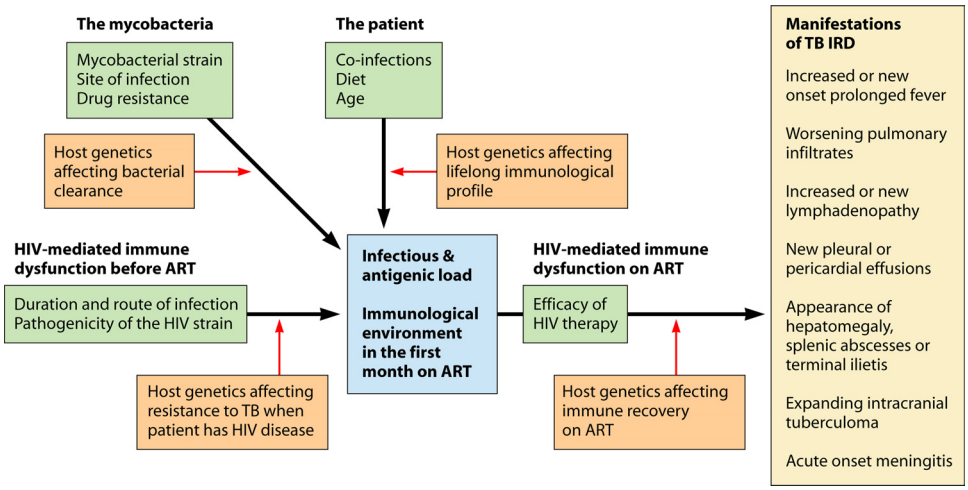

FIG. 1. Pathways to mycobacterial IRD. Elucidation of the events leading to an IRD must begin with determinants of the patient's mycobacterial disease, his or her innate immune capacity, and the immunological changes caused by HIV disease (green boxes). Whether the resultant antigenic burden and immunological scenario (blue boxes) lead to a particular IRD depends on the immunological response to therapy. Each stage can be modified by the patient's genetic profile (orange boxes).

With careful case definitions, retrospective genetic studies can efficiently aid in the identification of pathways involved in the pathogenesis of IRD and the development of diagnostic algorithms. It is important to recognize that an IRD is the consequence of circumstances established over several years, so genotypes may associate with IRD through effects on susceptibility to the underlying infection or through the degree of immunodeficiency before ART (Fig. 1).

MYCOBACTERIUM TUBERCULOSIS IRD: ALWAYS AN EXAGGERATED IMMUNE RESPONSE, BUT DIFFERENT MANIFESTATIONS SUGGEST DISTINCT MECHANISMS

Mycobacterium tuberculosis is the most common pathogen associated with IRD (61, 99). Worsening of existing lesions or the appearance of new lesions during treatment of tuberculosis (TB) has been recognized in HIV-negative patients for many years (11), with most reported cases associated with lymph node TB (17). These "paradoxical" TB exacerbations are more common in patients coinfected with HIV and have a wide spectrum of presentations, ranging from mild lymph node inflammation to potentially fatal disease of the CNS. They are more frequently related to the initiation of potent ART than to antitubercular therapy (ATT) (102). Paradoxical worsening of TB in HIV patients probably reflects a restoration of pathogen-specific cellular immune responses (51), as discussed later.

In a clinical setting, TB-associated IRD (TB-IRD) must be differentiated from failure of ATT, drug toxicities, new opportunistic infections, nonresponse to ART, and nonadherence to treatment. The distinction is critical for HIV clinics in countries with a high burden, where it may impact the scaling up of ART services (77, 99). A reliance on case definitions incorporating clinical and laboratory parameters for confirmation of diagnosis is one of the many challenges of TB-IRD (89, 100). Recognition of the phenomenon is essential to minimize shifts to second-line antitubercular or antiretroviral regimens.

Retrospective and prospective studies report that 7 to 43% of patients with HIV-TB coinfection develop IRD (11, 13, 15, 71, 77, 102, 104, 128, 129, 149), beginning as early as 5 days after starting ART (116). Most patients develop symptoms within the first 2 to 6 weeks (71, 77, 104, 128, 129), though cases may occur after 1 to 4 years (58, 62, 129).

There are two major presentations of TB-IRD. There may be clinical deterioration of TB disease in patients already receiving ATT when they begin ART, or IRD may reflect the presentation of TB that was subclinical before initiation of ART. Based on these observations, the International Network for the Study of HIV-Associated IRIS has defined two major categories—paradoxical TB-associated IRIS and ART-associated TB. A subset of the latter group is defined as cases of "unmasking TB-associated IRIS." Patients with this scenario are those not receiving ATT when ART is initiated but presenting with active TB within 3 months of starting ART. They may experience severe clinical manifestations or a clinical course complicated by a paradoxical reaction when started on ATT (93).

TB-IRD can affect many sites in the body (Table 1; Fig. 1). Two studies describe TB-IRD in lymph nodes alone (71, 128), while several studies show diverse manifestations (11, 13, 15, 61, 77, 99, 102, 129). Pulmonary and intra-abdominal diseases are common (13, 15, 77, 129). Clinical manifestations of IRD depend on the site of the TB, though immune recovery events may be more acute than expected in the usual course of TB (30). IRD in a TB patient may present as prolonged, high-grade fever or the reappearance of fever, worsening pulmonary infiltrates (Fig. 2), new pleural effusions, or increased or new lymphadenopathy. Many patients initially treated for pulmonary TB develop additional manifestations of IRD at extrapulmonary sites (77). Hepatomegaly, lymphadenopathy (mediastinal, cervical, or abdominal), splenic abscesses, terminal ileitis leading to perforation, arthropathy, and cutaneous lesions are manifestations of TB-IRD, with or without exacerbation of existing TB disease (13, 77, 102). Acute respiratory distress syndrome (ARDS), cystic lung disease, pericardial effusion

TABLE 1. Clinical manifestations of TB-associated IRD

Clinical manifestation	Reference(s)
Fever (prolonged, high grade)	11, 99, 129, 150
Worsening pulmonary infiltrates	51, 77, 99, 129
Pleural effusion	99, 129
Increased or new lymphadenopathy	51, 77, 129, 149
Intra-abdominal manifestations—ascites, splenic abscesses, intra-abdominal lymphadenopathy, terminal ileitis with perforation, and peritonitis	77, 99
Acute respiratory distress syndrome	137
Cystic lung disease	122
Pericardial effusion with pericarditis	119
Psoas abscess	150
CNS manifestations—expanding intracranial tuberculomas and acute-onset tubercular meningitis	11, 34, 35, 118, 120, 149

with pericarditis, psoas abscess, and meningitis are less common manifestations of TB-IRD (35, 119, 122, 136, 149). Neurological disease following initiation of ART due to inflammation associated with previously silent *M. tuberculosis* infection in the CNS is a particular concern and may have a poor outcome (93). Several studies describe expanding intracranial tuberculomas (11, 34, 35, 118, 120, 148), and acute onset of TB meningitis has been reported (35).

A low baseline CD4 T-cell count, a shorter interval between TB diagnosis and ART initiation, and disseminated or extrapulmonary TB have been proposed as risk factors for TB-IRD. In a prospective study of 423 South African patients, most IRD cases were due to TB, and low baseline CD4 T-cell counts were the only independent risk factor for IRD (99). This confirms another South African study and a study from the Johns Hopkins HIV clinic (77, 87). Increased risk of TB-IRD in patients with low CD4 T-cell counts may be related to a higher bacillary burden (66). However, prospective studies from the United States and the United Kingdom (11, 15) and a retrospective study from India (71) found no association between baseline CD4 T-cell count and TB-IRD. Extrapulmonary and disseminated TB cases are also associated with a higher risk of IRD (11, 15, 88). Early initiation of ART after TB diagnosis was a strong risk factor for developing TB-IRD in several studies (11, 77, 93). A modeled decision analysis tree using data from many published studies predicted the highest rates for patients initiated on ART within 2 months of ATT initiation (125).

In deciding when to initiate ART in patients being treated for active TB, the risk of IRD must be balanced against considerations of pill burden, drug-drug interactions, and overlapping toxicities (16, 36). Case fatality rates for patients with TB during the first 2 months of TB treatment are high, particularly in settings with a high prevalence of HIV

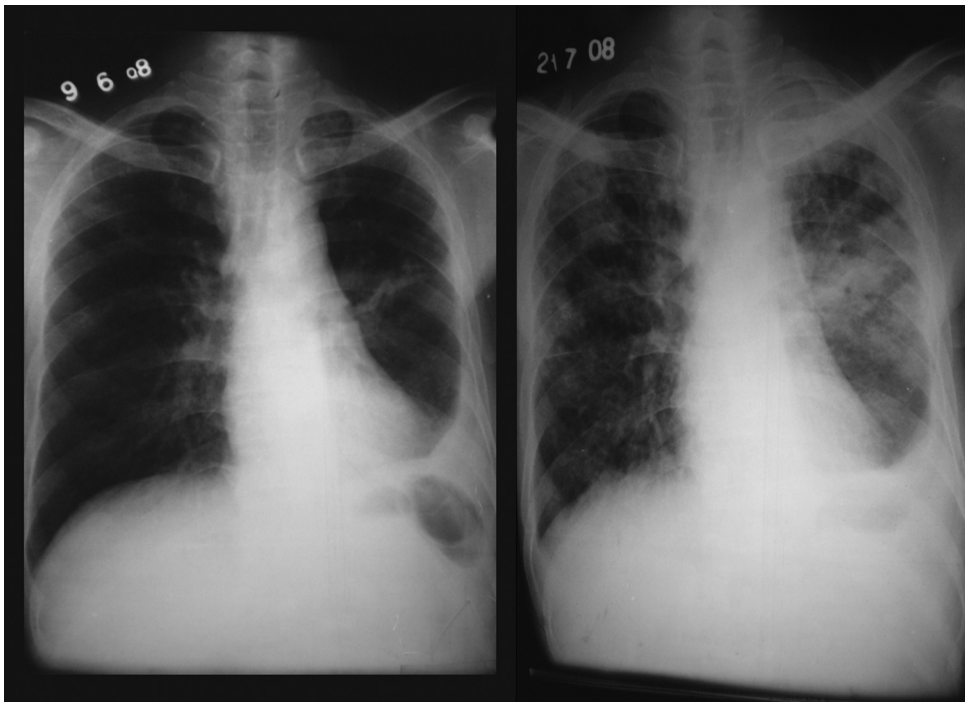

FIG. 2. Pulmonary TB IRD. The images are X-ray radiographs for a male patient (aged 38 years) displaying a parenchymal lesion in the left lung/left midzone and left pleural effusion when initiated on ART 6 weeks after starting TB therapy (left). Exacerbation of clinical symptoms after 3 weeks coincided with increased pulmonary infiltrates (right).

(32, 78), suggesting that ART should begin early. There is evidence that active TB and ATT do not compromise immunological and virological responses to ART (12, 89). SAPIT is a large clinical trial designed to determine the optimal timing of ART initiation. In the sequential-treatment arm, patients started ART soon after completing their TB treatment. This arm was stopped in September 2008, as the mortality rate was double that in integrated-treatment arms, where patients started ART during TB treatment (http://www.caprisa.org/joomla/index.php/component/content/article/98). Overall, available data favor initiating ART early once the patient has stabilized on TB treatment (despite the risk of TB-IRD), especially for persons with CD4 T-cell counts of <200/μl, among whom there is a high mortality rate (153).

Most cases of TB-IRD are self-limiting (77), and many patients need no change or only minor changes in treatment. This may include nonsteroidal anti-inflammatory drugs, although there are no direct data to support their use. Moderate to severe cases usually respond to steroids, and occasionally interruption of ART may be needed. In the first randomized trial addressing TB-IRD, prednisolone (1.5 mg/kg of body weight for 2 weeks and then 0.75 mg/kg for a further 2 weeks) was associated with a significantly reduced need for hospitalization and medical procedures in patients with mild to moderate TB-IRD (95). Severe manifestations, such as spleen rupture, compressive lymphadenopathy causing dyspnea, ureteral compression, and thrombo-embolic events, may require hospitalization and surgical interventions (13, 15, 77). Needle aspiration, surgical drainage, or laparotomy for severe abdominal manifestations are rarely required. Despite the short-term morbidity associated with severe IRD, the long-term outcome is usually good (13, 129). A few deaths (4 to 10%) are reported, mostly for patients with very low CD4 T-cell counts and disseminated TB disease, including pulmonary, intra-abdominal, and bone marrow involvement (15, 77).

Despite these comprehensive clinical and epidemiological data, few studies have addressed the cause of the immunopathology, and several of these are based on IRD caused by nontuberculous mycobacteria. Although these cases can resemble TB-IRD presenting as lymphadenitis, the diverse manifestations of HIV-TB in resource-constrained settings suggest diverse pathological mechanisms. Tissue inflammation, granuloma formation, and occasionally hypercalcemia characterize most IRD associated with nontuberculous mycobacteria (48, 84) and *M. tuberculosis* (63, 79, 102), consistent with the observed restoration of DTH responses to mycobacterial antigens. A role for effector T cells is suggested by the increase in purified protein derivative-specific Th1 IFN-γ-producing T cells and Th1 cytokines in IRD patients studied in France (9). This was confirmed with several mycobacterial antigens in a large cross-sectional cohort from South Africa (94).

The important role of regulatory T cells (Treg cells) in the maintenance of immune homeostasis has led to the hypothesis that quantitative or functional defects in Treg cells may promote TB-IRD (52, 68). However, the number of Treg cells was not reduced in a small group of TB-IRD patients studied longitudinally in Malaysia or in a larger cross-sectional cohort from South Africa. Treg cell function was not investigated in either study (94, 138). Interleukin-10 (IL-10) can suppress IFN-γ production and DTH responses to mycobacterial antigens (10, 37, 44). Thus, TB-IRD may be a consequence of ART restoring a CD4 T-cell response to mycobacterial antigens that results in a relative deficiency of IL-10 or other regulatory cytokines compared with IFN-γ. A relative reduction in IL-10 responses was demonstrated for two patients with IRD caused by nontuberculous mycobacteria (82). Seddiki et al. (127) described increased numbers of Treg cells but impaired IL-10 production in similar cases.

The critical role of macrophages in both TB and HIV infection, the rapid onset of symptoms of TB-IRD, and poor increases in peripheral CD4 T-cell counts in some affected patients suggest that recovery of macrophage function in patients on ART may result in disordered immune responses and TB-IRD (145). In one case of unmasking TB-IRD, a lung biopsy demonstrated bronchiolitis obliterans organizing pneumonia. Immunohistochemistry revealed abundant $CD68^+$ cells and few T cells, consistent with a predominantly macrophage infiltrate (80). Others suggested that differential reconstitution of myeloid dendritic cell (DC) function may lead to a pathogenic predominance of Th1 immune responses (39).

CRYPTOCOCCAL IRD: SEVERE CONSEQUENCES OF A HIGH ANTIGEN LOAD IN THE CENTRAL NERVOUS SYSTEM

Cryptococcal IRD may present either as a paradoxical relapse, secondary to restored immunity to partially treated infections or residual cryptococcal antigens (8, 69), or as the unmasking of a subclinical infection present at the time of ART (152). Cryptococcal IRD affects 19 to 50% of patients initiating ART with a prior diagnosis of cryptococcal disease (4, 67, 81, 130). Risk factors for the development of cryptococcal IRD include initiation of ART within 30 to 60 days of cryptococcal diagnosis, previously unknown HIV infection, fungemia, and very low CD4 T-cell counts (130, 137). A distinct feature of cryptococcal IRD is its association with substantial morbidity and mortality, arising from involvement of the CNS. Although some cohorts report low mortality (84), associated morbidities are significant and include seizures, hemiparesis, and dysarthria. In other cohorts, mortality ranged from 9% to as high as 66%, illustrating the severity of this form of IRD (67, 81, 130).

To understand why cryptococcal IRD is associated with high rates of morbidity and mortality, one must examine the immunopathological potential of cryptococci. Even without IRD, acute mortality of cryptococcal meningitis in the developed world is 10 to 25% (106). A feature of the organism that may explain this virulence is its polysaccharide capsule (70). It is composed primarily of two polysaccharides, glucuronoxylomannan (GXM) and galactoxylomann, where GXM contributes ~88% of the capsular wall (26). GXM stimulates monocytes via CD14 and Toll-like receptor 4, inducing translocation of NF-κB to the nucleus, but the pathways necessary for protective tumor necrosis factor alpha (TNF-α) production are not stimulated (131). This fits evidence that capsule-deficient *Cryptococcus neoformans* mutants are less virulent than native strains (3, 22, 23).

Capsule-specific immunomodulatory functions include antiphagocytosis, complement depletion, inhibition of leukocyte migration, and dysregulation of cytokine secretion in the in-

fected host (18). GXM polysaccharide can inhibit T-cell proliferation and cell-mediated immune responses directly (155). In mice, cryptococci cross the blood-brain barrier of cortical capillaries and the brain parenchyma and seed the leptomeninges with cortical "microcysts" within 6 h (25). Hence, *C. neoformans* is poised to generate high antigen burdens in a distinct immunological compartment, especially in immunocompromised HIV-infected patients.

It is accepted that mycobacterial IRD result from restored antigen-specific immunity following ART. A similar model for cryptococcal IRD is now supported by small immunological studies documenting IFN-γ responses to cryptococcal antigen. The number of cryptococcus-specific T cells in the peripheral blood compartment and the level of serum antibody to cryptococcal antigens were increased in patients experiencing the syndrome (138). Restored immunity to cryptococcal antigens within the CNS is likely responsible for the dramatic clinical presentations of cryptococcal IRD, but samples have not been available to demonstrate this hypothesis.

Cases of cryptococcal IRD are often referred to as "relapsing" or "paradoxical," whereby the onset of IRD occurs despite successful antifungal therapy with amphotericin B and/or fluconazole (8, 67, 69, 102). In contrast to the unmasking form of cryptococcal IRD, relapsing cases are culture negative, supporting the hypothesis that residual cryptococcal antigen is the precipitating factor. Higher opening cerebrospinal fluid (CSF) pressures are observed in cryptococcal IRD patients (67, 130, 154). These may reflect delayed clearance of residual antigen from the leptomeninges and the precipitating inflammation induced by a Th1 response following ART. While the identification of predictive markers for cryptococcal IRD is desirable, measurements of serum or CSF cytokine profiles are likely to vary between individuals, so no single test (e.g., CSF cryptococcal antigen titer) is likely to uniquely predict cryptococcal meningitis IRD.

Therapy for cryptococcal IRD is complex. Paradoxical cryptococcal IRD is usually associated with culture-negative CSF findings (67, 130, 137) and higher CSF opening pressures than those in non-IRD cryptococcal meningitis patients (45 versus 31 cm H_2O) (130). In HIV-infected patients experiencing non-IRD cryptococcal meningitis, high pretreatment opening pressure (>25 cm H_2O) or an increase in CSF pressure of >1 cm H_2O after 2 weeks of treatment are associated with a poorer clinical outcome (56). Therefore, therapeutic CSF drainage can be recommended in cryptococcal IRD cases with opening pressures of >25 cm H_2O (124). A recent study supports the use of early ART in HIV-infected patients with acute infections, regardless of the underlying opportunistic infection (158). Continuation of ART in the setting of paradoxical cryptococcal IRD is usually associated with favorable outcomes (130, 137). However, in some cases of cryptococcal IRD meningitis, profound CSF inflammation is manifested by sustained high CSF pressures and a poor clinical response to antifungal therapy. The administration of corticosteroids and discontinuation of ART to reduce meningeal inflammation and neurological symptoms may assist in cases of aseptic paradoxical cryptococcal IRD with documented multiple negative CSF cultures. The duration of antifungal therapy is critical, as the time to sterilization of CSF ranges from 21 to 64 days depending on the fluconazole dose and antifungal regimen (59, 74, 96).

TABLE 2. Historical or prospective cohort studies of VZV IRD

Reference	No. of patients	Incidence of VZV disease (%)	Time to onset after commencing ART (wk)
90	193	7	86% within 16
53	132	6	2–26 (62.5% within 17)
40	316	8	All within 17
140[a]	61	11.5	All within 24
42	115	12	4–60
116	153	5	2–21 (83% within 16)[a]
120	199	9	Median, 14 (interquartile range, 8 to 22)

[a] Studies undertaken with children.

IRD ASSOCIATED WITH HSV OR VZV INFECTION MAY BE MEDIATED BY CYTOTOXIC LYMPHOCYTES

Inflammation developing at sites of persistent infection by herpes simplex virus type 1 or 2 (HSV-1 or HSV-2) or by VZV after commencement of ART often has characteristics of IRD (52, 53). It commonly presents during the first 4 months of therapy, is associated with a decrease in HIV replication, and may have atypical and/or severe disease manifestations. Though the evidence is mostly indirect, the inflammation probably reflects restoration of an immune response against HSV or VZV antigens.

Following the introduction of ART in the mid-1990s, cases of dermatomal herpes zoster were up to five times more common in patients who had recently commenced ART (1, 90). Cohort studies of adults and children indicated that the incidence of VZV disease ranged from 5 to 12%, with most cases occurring in the first 16 weeks of therapy (Table 2). A low CD4 T-cell count was a risk factor in children (140) but not in adults (40, 42, 90). VZV disease after commencement of ART usually presents as shingles affecting a single dermatome but may present as multidermatomal shingles, Ramsay-Hunt syndrome (M. A. French, personal observations), or myelitis (20, 29).

HSV disease affects about 5% of children or adults who commence ART (53, 116). An incidence of 50% in one publication may reflect data collected from a clinic specializing in genitourinary medicine (121). In children, HSV disease after ART affects mainly the face (116), whereas in adults it is mainly anogenital (53, 121). This may reflect a predominance of HSV-1 infection in individuals who are not sexually active. Anogenital and facial HSV disease after ART often presents with typical lesions, but ulceration may be abnormally persistent and lesions may become necrotic and/or hemorrhagic. Encephalitis and myelitis associated with definite or presumptive HSV infection are rare presentations of IRD but are important because permanent neurological disability or death may result (53, 116).

An interesting form of HSV IRD has been described for negroid men. Fox et al. (48) described three men from Uganda who commenced ART with CD4 T-cell counts below 50/μl and within 6 months developed chronic inflammatory lesions on the penis associated with HSV infection. The histopathology of lesions was atypical for genital HSV disease, as there was a prominence of plasma cells and eosinophils. One author (M. A. French) has investigated a Zimbabwean negroid man who developed a similar chronic inflammatory lesion on the penis after commencing ART.

He had a pretreatment CD4 T-cell count of 6/μl, and histological examination showed plasma cells and eosinophils. Chronic ulceration or hypertrophic lesions of the vulva in Zimbabwean negroid women after commencement of ART might have a similar etiology (121, 156).

NK cells and CD8 T cells play a major role in the immune response to viruses that cause persistent infections, including VZV and HSV. VZV IRD has been associated with an increase in circulating CD8 T cells after 1 month on ART (90) or 1 month before the onset of herpes zoster (40). However, circulating CD8 T cells were lower than the baseline 3 months after ART in children with VZV IRD (140). Preliminary data associate the use of ART in HIV-infected patients coinfected by HSV with an increase in circulating effector and/or effector-memory T cells (detected by IFN-γ enzyme-linked immunospot assay), but it is not possible to determine the contribution of CD8 T cells (117). A case study of myelitis resulting from VZV IRD demonstrated a predominance of activated NK cells and CD8 T cells in the CSF (29).

Treatment of HSV or VZV IRD requires appropriate therapy to suppress replication of the opportunistic virus and to reduce antigen load. Although data from clinical trials are lacking in the context of IRD, corticosteroid therapy should also be considered for dermatomal zoster, to reduce the risk of subsequent neuralgic pain, and in VZV or HSV IRD of the CNS when there is a risk of permanent neurological sequelae or death (29, 51, 116). Topical corticosteroid therapy to an eye given under the supervision of an ophthalmologist may be indicated for ophthalmic zoster.

IRD MANIFESTED AS CMV RETINITIS OR VIRAL ENCEPHALOMYELITIS: A SEARCH FOR THE CYTOKINES

In HIV-infected patients responding to ART, cytomegalovirus (CMV) retinitis may recur within a few weeks, with a clinical presentation similar to that seen in patients with AIDS. Over a longer time span, some patients also experience immune recovery uveitis (IRU), presenting as ocular inflammation (vitritis, macular edema, or formation of epiretinal membranes) and decreased vision. Most IRU patients also have a history of treated CMV retinitis before ART (126). Studies of patients who began ART in Western Australia before 1998 associated CMV retinitis and/or encephalomyelitis experienced during immune recovery on ART (CMV/encephalitis IRD) with a common major histocompatibility complex haplotype (HLA-A2, B44, TNFA-308*2, DR4) (114), suggesting similar immunopathological mechanisms. Two cases of viral encephalomyelitis were treated successfully with corticosteroid therapy, suggesting an immunopathological etiology (51). We subsequently associated CMV/encephalitis IRD with high and rising levels of plasma IL-6 and sCD30 (133, 134). At the time, this was associated with a Th2 cytokine environment, but subsequent data shed doubt on this interpretation of elevated sCD30 (111).

The need for prospective collection of PBMC, CSF, or vitreous fluids delayed further immunological studies, but some insights were gained from genetic associations. Briefly, carriage of IL12B(3′UTR) allele 1 and/or TNFA-308 allele 2 was associated with CMV/encephalitis IRD (113), and CMV/encephalitis IRD occurred in patients with nadir counts below 30 CD4 T cells/μl (112). Moreover, carriage of IL12B(3′UTR) allele 1 and/or TNFA-308 allele 2 was associated with very low nadir CD4 T-cell counts among patients who began treatment with CD4 T-cell counts of <100/μl (irrespective of IRD) (P. Price, unpublished data). Hence, the *IL12B* and *TNFA* genotype may affect whether a patient attains a very low nadir CD4 T-cell count or survives this nadir. Such patients are at risk of CMV/encephalitis IRD.

The question remains of whether CMV/encephalitis IRD are mediated by T cells, NK cells, antibody, monocytes, or CMV itself. Among CMV-seropositive patients starting ART in Taiwan, CD4 (but not CD8) T-cell responses to CMV were lowest in the three patients who developed CMV retinitis (60). West Australian CMV/encephalitis IRD patients had poor responses to CMV antigen 2 to 4 years after their IRD (114). Indeed, nadir counts below 30 CD4 T cells/μl were associated with low CD4 T-cell IFN-γ responses to CMV antigen and higher IFN-γ production by NK cells after long periods on ART (115). Moreover, CMV/encephalitis IRD and CMV during AIDS occurred in patients with large numbers of activating KIR genes (112). These data do not favor a CD4 T-cell response as a driving mechanism but suggest a role for NK cells. However, NK cells are implicated in protective responses to CMV, and their induction suggests that there is active viral replication.

The role of CMV replication in the pathogenesis of CMV IRD is unclear. A single positive test demonstrating viremia poorly predicts CMV retinitis in AIDS patients (151), but there may be an association for patients on therapy (19). One case study describes a patient with multiple recurrences of CMV retinitis while on ART, associated with active CMV replication in plasma and vitreous fluid. The patient had no lymphoproliferative response to CMV but responded to *Candida*, suggesting a level of immune recovery (65). We are investigating two CMV retinitis IRD patients being treated in Kuala Lumpur. One experienced CMV viremia (monitored by PCR), and both had a small increase in CMV antibody with no clear T-cell IFN-γ responses to CMV antigen. This pattern was also seen in 50% of the non-IRD patients tested (Y. K. Yong, D. B. A. Tan, A. Kamarulzaman, and P. Price, unpublished data). NK and CD8 T-cell responses are now being assessed, but it is possible that responses of PBMC will not be informative in this context. The appearance of CMV-reactive antibody warrants further mention, as increases were mostly confined to CMV IRD patients in the West Australian group (133) but were broadly observed in Kuala Lumpur. The enzyme-linked immunosorbent assay used was standardized across the study sites, so the difference may reflect CMV therapy before ART.

Few papers have addressed intraocular CMV replication and immune responses. In eyes collected at autopsy from AIDS patients, CMV replication (assessed via expression of IE2) upregulated expression of FasL by retinal pigment epithelial cells (27). Such cells could induce apoptosis in activated (Fas^+) infiltrating leukocytes and other retinal cells. This capacity could persist after viral replication ceased and could contribute to IRD. Two studies demonstrated T-cell activity without active CMV replication in IRU. Schrier et al. (126) compared fluids from eyes with IRU and those with CMV retinitis (collected pre-ART and CMV DNA positive). TNF,

IL-4, and several chemokines were undetectable, but samples from eyes with IRU contained less IL-6 and more IL-12 than those from eyes with CMV retinitis. Since our data implicated an *IL12B* and an activating KIR genotype, this finding is intriguing. It may be important that CMV carries several proteins able to subvert protective NK cell responses (150). This includes UL18, a molecule able to stimulate or suppress NK-cell-mediated killing, depending on expression of LIR-1. Another candidate is UL40, which encodes a peptide identical to the leader sequence of HLA-E. This enhances expression of HLA-E, which is an inhibitory ligand of CD94/NKG2a. HLA-E-restricted CD8 T-cell responses have been demonstrated in healthy donors (92). Mutimer et al. (101) created CD4 and CD8 T-cell clones from the vitreous humor of one patient. The CD4 T-cell clones were not CMV reactive, and the CD8 T-cell clones did not recognize known protective antigens from CMV (pp65, pp150, IE-1, or gB). HLA-E restriction and UL40 were not discussed, and few studies will access vitreous humor over the next few years. If studies of PBMC do not prove informative, then the pathogenesis of CMV IRD may remain obscure.

IRD ASSOCIATED WITH JCV INFECTION OF THE BRAIN

Progressive multifocal leukoencephalopathy (PML) of the brain is an immunodeficiency disease in patients with AIDS, reflecting the failure of immunological control of JC polyomavirus (JCV) infection of oligodendrocytes and astrocytes (54). It is characterized by a paucity of inflammatory cells in brain lesions. Potent ART can resolve the brain lesions, presumably because cellular immune responses against JCV antigens are augmented. However, introduction of ART may exacerbate established PML or promote its presentation (28, 46, 139). These presentations of PML are often atypical in that imaging studies demonstrate inflammatory changes (46) and brain biopsies demonstrate inflammatory cell infiltrates with a prominence of CD8 T cells (98, 146). Since these findings suggest that the inflammation reflects restoration of a CD8 T-cell response against JCV antigens, exacerbations and first presentations of PML in patients on ART can be considered paradoxical and unmasking forms of IRD, respectively. Some studies call the paradoxical form PML-delayed IRIS and the unmasking form PML-simultaneous IRIS (139).

Cohort studies of HIV patients show that 19 to 23% of PML cases are paradoxical or unmasking IRD (28, 46). An analysis of cases from one center and those published previously demonstrated a median time of onset of 7 weeks. Most cases occurred within the first 3 months of ART, but a few were as late as 26 months (139). Paradoxical JCV IRD tended to occur earlier than unmasking JCV IRD. Mortality rates were 52.9% for paradoxical JCV IRD and 31.3% for unmasking JCV IRD. These are similar to those reported for meningitis resulting from cryptococcal IRD, emphasizing the seriousness of IRD of the CNS.

Predictors of JCV IRD have not been identified (46), and no evidence-based guidelines for treatment are available. A recent review found no beneficial effect of corticosteroid therapy (139).

IRD MAY PRESENT AS LEE FOLLOWING INITIATION OF ART IN HIV-HBV-COINFECTED PATIENTS

Liver enzyme elevation (LEE), defined as an increase in the plasma ALT level, is sometimes observed in patients with HIV and hepatitis B virus (HBV) coinfection after ART is commenced. Some studies also use the term hepatic flare. A definition for LEE that is commonly adopted is five times the upper limit of normal or a rise of over 100 IU/ml from baseline. LEE in patients coinfected with HIV and HBV after commencement of ART may reflect worsening of underlying liver disease, antiretroviral hepatotoxicity, other medications, opportunistic infections, or an IRD (7). A recent retrospective cohort study associated LEE following ART in HBV- and HCV-coinfected patients with the overall increase in CD4 T cells (103), consistent with a role for immune reconstitution in pathogenesis.

Lamivudine, tenofovir, and emtricitabine are active against both HIV and HBV. Coinfections are usually treated with two HBV-active agents, including tenofovir (83, 91). LEE was observed in 25% of 36 ART-naïve HIV-HBV-coinfected patients in a prospective randomized clinical trial of HBV-active ART (lamivudine versus tenofovir versus lamivudine-tenofovir) in the Tenofovir in Coinfection (TICO) study in Thailand (91). Individuals had advanced HIV infection (median CD4 T-cell level, 36 CD4 T cells/μl), and those developing LEE had significantly higher HBV DNA and ALT levels before ART. A randomized prospective study of adefovir and tenofovir in HIV-HBV-coinfected patients estimated a similar rate of LEE, even though individuals were on stable ART at enrollment (107).

HBV IRD is sometimes followed by anti-HBe, and even anti-HBs, seroconversion. In the TICO study, many patients developed anti-HBe and anti-HBs antibodies, 33% lost HBeAg, and 8% lost HBsAg (91). A community-based study of HIV-HBV-coinfected patients in France found that individuals with more advanced HIV infection were more likely to acquire anti-HBe or anti-HBs antibodies. HBV viremia often declined following ART, even without HBV-active drugs (97). Hence, the restoration of immunocompetence in patients on ART may control chronic HBV infection and drive seroconversion. Hepatic decompensation is a recognized complication of HBV IRD in patients with underlying cirrhosis and may be fatal (41). LEE can follow initiation of ART in the setting of occult HBV infection (HBsAg negative and HBV DNA positive). This may represent an IRD (47, 109).

An increase in hepatic transaminases or hepatotoxicity in the setting of HBV infection is immunologically mediated, as HBV is a noncytopathic virus. LEE during HBV therapy is relatively common in HBeAg-positive individuals and is characterized by a substantial elevation in serum ALT before or during seroconversion to HBeAg, with a reduction in HBV DNA. Repeated hepatitis flares or continuous recruitment of inflammatory cells to the liver leads to fibrosis, cirrhosis, and possible hepatocellular carcinoma (reviewed in reference 21).

Presentation of HBsAg and HBcAg peptides by major histocompatibility complex class I molecules on infected hepatocytes leads to activation of cytolytic CD8 T cells, which can lyse infected hepatocytes and may damage surrounding tissues. Patients with high HBV viral loads had fewer intrahepatic CD8 T

cells than those controlling HBV replication (85), so these cells may be protective. However, infiltration of non-HBV-specific cells may dilute the HBV-specific cells in severe infections. Inflammatory liver injury may then reflect FasL expression by Kupffer and lymphoid cells and increased granzyme-mediated cytolytic activity of cells in portal areas (139). HIV and HBV can trigger apoptosis of infected hepatocytes through the TNF-related apoptosis-inducing ligand (TRAIL) pathway (6), and IFN-γ can trigger production of chemokines such as CCL3, CCL4, CCL5, CXCL9, and CXCL10. These mediate recruitment of mononuclear cells to the liver and activate HBV-specific cytolytic CD8 T cells and cells such as neutrophils, monocytes, NK cells, and iNKT cells, leading to hepatocyte damage and LEE (132). Case-control studies associated hepatitis flares in HBV monoinfection with elevated plasma IFN-α, IL-18, IL-6, and IL-2 levels (45) or IL-8 and IFN-α levels (43).

Since the clinical presentation of HBV IRD in HIV-HBV coinfection can resemble spontaneous hepatitis flare in HBV monoinfection, the pathogenesis may also be similar. A recent prospective study associated LEE following initiation of HBV-active ART with elevated plasma CXCL10, IL-18, and sCD30 levels (33). CXCL10 is a chemoattractant for T cells, NK cells, and monocytes, so persistent elevation of CXCL10 in the setting of a rising CD4 T-cell count may drive T-cell recruitment to the liver and result in hepatocyte damage (141). sCD30 was described as a marker of a Th2 cytokine environment, but its levels in HIV patients may reflect T-cell activation rather than a bias toward the production of IL-4 over IFN-γ (111). There was no clear association between TRAIL expression on NK cells and LEE in HIV-HBV-coinfected individuals (33), but this was observed in hepatitis flares seen in HBV monoinfection (43).

HBV IRD may reflect dysregulated restoration of HBV-specific CD8 and CD4 T-cell responses. HBV-specific CD8 T-cell responses recover in patients on ART, but this has not been related to LEE (75, 76). A lack of HBV-specific CD4 T-cell help in HIV-HBV-coinfected individuals may lead to an inefficient or dysregulated HBV-specific CD8 T-cell response and/or a greater role for innate immunity (24). Treg cells may modulate immune responses to HBV (49), but Treg cells have not been studied in the setting of LEE following ART in HIV-HBV-coinfected individuals.

ART MAY ALLOW IMMUNOLOGICAL CONTROL OF HCV, BUT THIS MAY DAMAGE THE LIVER

Various types of evidence suggest that LEE after commencement of ART in patients with HIV and HCV coinfection might also result from IRD in the liver. A recent retrospective study demonstrated a reduced risk of hepatotoxicity following ART in HIV-HCV-coinfected patients if they achieved a sustained virological response with IFN-based therapy before commencing ART (72). In a retrospective study of coinfected patients who underwent liver biopsy, the risk of LEE was greatest in patients with advanced fibrosis (5). Several studies associate LEE with carriage of HCV genotype 3 and note that patients with genotype 3 have a favorable response to IFN-based therapy (143). They speculate that genotype 3 may be optimally immunogenic.

Antiretroviral drugs have no direct anti-HCV activity, so HCV RNA levels usually remain unchanged or increase briefly after initiation of ART (147, 159). However, clearance of HCV has been described, though this is a rare event in HCV monoinfection. Clearance of HCV following ART was associated with an early fall in HIV RNA levels and with increases in the numbers of CD4 and CD8 T cells. In rare cases, this was accompanied by clinical hepatitis (38, 105, 157). HCV IRD more commonly presents as LEE in patients on ART without resolution of HCV infection. John et al. (64) described three cases of symptomatic hepatitis in HIV-HCV-coinfected individuals after initiation of ART containing an HIV protease inhibitor. In one patient, HCV RNA increased transiently and otherwise remained unchanged. Two patients were previously HCV antibody negative (HCV RNA positive) and developed HCV antibody at the time of LEE, supporting the role of immune reconstitution in this setting.

Chronic HCV infection is associated with a weak and narrowly focused HCV-specific CD8 T-cell response (31). In acute self-limiting infection, HCV clearance correlates with production of IFN-γ and a strong HCV-specific CD8 T-cell response (57), which may invoke liver damage (45, 142). Numbers of intrahepatic CD4 T cells are reduced in HIV-HCV coinfection, but intrahepatic HIV-specific CD4 and CD8 T cells may produce more TNF-α than IFN-γ (144). An increase in ALT in HIV-HCV-coinfected patients following ART correlates with elevated total CD8 T-cell numbers (55). High plasma CXCL10 concentrations and abundant CD8 T cells expressing its ligands (e.g., CXCR3) are a hallmark of active HCV monoinfection and resolve with successful therapy (73). CXCL10 levels are also high in coinfected patients (123) and correlate with indices of liver damage. Studies of HCV IRD will be informative.

Abnormal production of proinflammatory cytokines (IL-8, TNF-α, and IL-6) by monocytes and myeloid DC was identified for up to 1 year following initiation of ART in HIV-HCV-coinfected patients, but this was not related to HCV IRD (2). An increase in ALT in HIV-HCV-coinfected patients following ART correlates with increased levels of sCD26 and LAG-3 (markers of T-cell activation) (135; Price, unpublished data). Patients displayed increased levels of HCV core-reactive antibody but normal plasma IL-6, sTNFR, sCD30, and nitrate/nitrite levels. This favors T-cell rather than monocyte activation as the driver of HCV IRD but does not illuminate the role of Th1 or Th2 cytokines. The only available genetic study (113) established that HCV IRD is not associated with the same genetic profile as CMV IRD, so these appear to be mechanistically distinct.

CONCLUSIONS: SOME PIECES BELONG IN ANOTHER JIGSAW PUZZLE

Prospective and larger cross-sectional studies are now shedding light on the pathogenesis of TB IRD, but the multiplicity of clinical presentations suggests a range of pathogenic mechanisms. Moreover, the viral IRD appear to be distinct. The balance of evidence suggests a Th1 response driving hepatic inflammation associated with HBV and HCV, while CD8 T cells may be central to IRD associated with JCV and VZV. The immunological consequences of extreme immunodeficiency before ART appear to be critical in CMV IRD. NK cells

seem to be a more probable candidate under these conditions, possibly influenced by viral genes that can modify NK cell function. Elucidation of the many mechanisms underlying IRD will require prospective studies including samples collected at the initiation of ART and tissues affected by the IRD. Careful classification of patients and the selection of non-IRD patients controlling for asymptomatic opportunistic infections will be critical as we solve the puzzle(s).

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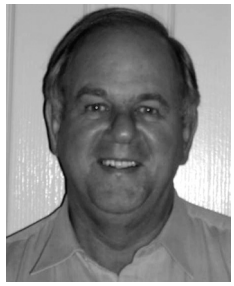
Patricia Price (Professor) began as a laboratory-based immunologist with an interest in problems facing the majority of the world—malnutrition, parasite infections, and, finally, viruses. Since 1996, she has undertaken several projects in mapping and characterizing polymorphic immunoregulatory genes in the central major histocompatibility complex—this has continued to include characterizations of tumor necrosis factor haplotypes associated with disease in Asians and Caucasians. She established a collaboration with Martyn French to investigate the immune responses of human immunodeficiency virus (HIV)-infected patients undergoing potent antiretroviral therapy (ART). This includes a search for markers which define immune restoration diseases (IRD) and reasons why some patients fail to restore CD4 T-cell numbers or function. The team now includes three postdoctoral scientists and several graduate students. Since 2004, collaborations have been established in Kuala Lumpur, Jakarta, Cambodia, Delhi, and Johannesburg to monitor immunological changes in HIV patients beginning ART with coinfections. Projects include those to study IRD and antiretroviral toxic neuropathy.

Upasna Agarwal is currently Head of the Department of Internal Medicine at LRS Institute of TB and Respiratory Diseases at New Delhi. Dr. Agarwal trained as an internist and has 10 years of clinical experience following her training. She is the physician in charge of the Antiretroviral Therapy (ART) Centre, an HIV clinic providing free antiretroviral treatment under the National AIDS Control Program, Government of India. The ART Centre has registered more than 600 HIV-infected patients for comprehensive HIV care, and about 250 patients have received expert consults on HIV-tuberculosis coinfection (HIV-TB) from this clinic. She has been instrumental in starting specialized HIV treatment care at the LRS Institute and is currently engaged in several clinical research projects in the field of HIV-TB. She has also been part of the national team for containment of avian influenza. Dr. Agarwal is married and has two children. She lives in New Delhi.

David Murdoch is a pulmonary clinician and Assistant Professor in the Department of Medicine at Duke University Medical Center. His clinical work has focused on the pulmonary complications of HIV infection in adults. After obtaining his master's degree in public health at the University of North Carolina at Chapel Hill, Dr. Murdoch contributed to defining the incidence of IRD in sub-Saharan Africa in a prospective South African study. His main area of expertise is in IRD in HIV patients, with a focus on TB-IRIS. He is currently undergoing basic science training in HIV immunology at the Duke University Center for AIDS Research (CFAR). He is involved in a number of studies with international collaborators examining the immunopathogenesis of IRD, with an emphasis on defining the activation, maturation, and regulation of T-cell subsets involved in the syndrome.

Julian Elliott is currently Assistant Head of Clinical Research at the Alfred Hospital Infectious Diseases Unit and HIV Clinical Advisor, Centre for Population Health, Burnet Institute. He was previously a technical advisor in HIV treatment, care, and research at the National Center in HIV/AIDS, Dermatology and STDs (NCHADS) of the Cambodian Ministry of Health, on secondment from the National Centre in HIV Epidemiology and Clinical Research (NCHECR) at the University of New South Wales. In that position, he contributed to the rapid expansion of HIV care in Cambodia and the establishment of an HIV research program. Dr. Elliott trained as an infectious disease physician and has worked in health care programs in other countries in Southeast Asia and in central Australian aboriginal communities. He has been a member of various Cambodian national committees, Australian aboriginal health working groups, and international program committees of Oxfam Australia.

Sharon Lewin is an infectious disease physician and a basic scientist. She is Director of the Infectious Diseases Unit at The Alfred Hospital; Professor of Medicine, Department of Medicine, Monash University in Melbourne; and codirector of the Centre for Virology, Burnet Institute, Melbourne, Australia. She completed her medical training at Monash University, followed by a Ph.D. in virology at the Burnet Institute in Melbourne and a postdoctoral fellowship at the Aaron Diamond AIDS Research Center, The Rockefeller University, New York. She heads a research laboratory that aims to understand why HIV and hepatitis B virus persist and evade the immune system. She is the immediate past president of the Australasian Society for HIV Medicine, the peak body in Australia that represents health professional and scientists who work in HIV medicine.



Martyn French is a clinical immunologist at Royal Perth Hospital and Professor of Pathology and Laboratory Medicine at the University of Western Australia, Perth, Australia. His clinical work and research activities have focused on the management of adults with acquired and primary immunodeficiency disorders for almost 30 years. He has conducted research on the immunology of HIV infection and has been an active participant in the Australian HIV Clinical Trials Programme for over 20 years. He is a past Chair of the Immune Based Therapies Working Group and is the current Chair of the Antiretroviral Working Group of The Australian National Centre in HIV Epidemiology and Clinical Research. His main area of expertise is IRD in HIV patients receiving ART. He first described IRD in HIV patients in the early 1990s and is currently undertaking research studies to define the immunopathogenesis of this group of disorders.