Introduction

Antiretroviral therapy (ART) confers enormous benefits to the majority of HIV-infected patients, resulting in remarkable improvements in HIV-related morbidity and mortality. This may be due in part to significant decreases in central nervous system (CNS) opportunistic infections [1–3]. A proportion of patients, however, develop immune reconstitution disease resulting in exuberant inflammatory responses to exogenous antigens, failure of immune recovery, or autoimmunity [4]. This syndrome has been described in association with a wide spectrum of infectious pathogens [5–11]. Immune reconstitution disease (IRD) has protean clinical manifestations, making definition difficult, and has been described by a number of terms including immune restoration disease, immune reconstitution disease and immune reconstitution inflammatory syndrome [5–11].

Various definitions for IRD have been published [5–12] and diagnostic criteria for CNS IRD have recently been proposed: worsening of neurological status; new or deteriorating neuroradiological findings; decrease in plasma viral load \( \geq 1 \times 10^5 \) copies/ml; presence of symptoms not explained by a newly acquired disease or by the usual course of a previously acquired illness; histopathology demonstrating T-cell infiltration [13]. The plasma viral load criterion is controversial as most ART naïve patients would initially be expected to respond to treatment and this criterion would limit use of the definition in resource-constrained settings.

The estimated incidence of IRD ranges between 15 and 45% [14] and a number of factors have been associated with an increased risk of developing IRD [5,6,9,15–18]. Most of the epidemiological data reported to date are retrospective, and large, prospective, observational cohort studies are required to define the incidence, clinical risk factors, immunological markers and outcome of IRD.

The paradoxical clinical deterioration seen with IRD is attributed to the recovery of the immune system on...
highly active antiretroviral therapy (HAART), which occurs in two phases [19,20]. IRD may occur during both phases of immune recovery, but most cases occur within 6 months of ART initiation [21,22]. The observed relationship with opportunistic infections indicates that the presence of microbial antigens may trigger the aberrant immune response [11]; this hypothesis is supported by the observation that inflammatory cytokines are elevated in patients with IRD [23]. Polymorphisms in cytokine genes may also play a role in genetic susceptibility to IRD [24]. The pathogenesis of CNS IRD is even more obscure than non-CNS IRD. In the reports of CNS IRD in which histopathological evidence is available, infiltrates of CD8 T cells have been described, although these cases were all associated with viral infections [25–33].

IRD is being described increasingly in association with a variety of CNS infections. Recognition of CNS IRD is difficult as the clinical presentation may mimic a variety of conditions including a new CNS infection, progression of infection due to antimicrobial/antiviral drug resistance, poor adherence to treatment, inadequate drug levels, or drug interactions/toxicities. Care must be taken to exclude these conditions before diagnosing CNS IRD as there may be therapeutic and clinical consequences. Exclusion of other causes of CNS deterioration may be difficult, particularly in resource-constrained settings. As ART becomes more readily available in developing countries, in which CNS infections are more common, CNS IRD may emerge as an important neurological complication of HIV therapy.

**JC virus**

JC virus (JCV), the cause of progressive multifocal leukoencephalopathy (PML), is the virus most commonly associated with CNS IRD. PML occurs in approximately 4% of untreated HIV patients [34]. PML IRD has been reported in two patient groups: patients with PML which paradoxically worsens after starting HAART [25–30,35–37] and patients whose PML only manifests after initiation of HAART [35–43]. The prevalence of PML presenting after commencement of HAART has been reported in PML case series as occurring in 6.5% (two of 31) [36], 8% (10 of 118) [41] and 19% (eight of 43) [40] of patients.

The presentation of paradoxical PML IRD is of deteriorating clinical and radiological findings, which typically occur 4–8 weeks, but sometimes up to 27 months, after commencing HAART [25,26,28–30,35–37,39]. MRI scans show progression of pre-existing lesions, with gadolinium contrast-enhancement, sometimes mass effect, and occasionally the development of new lesions [26–29,35–37,39]. In patients whose PML emerges after commencing HAART the median time to development of PML is approximately 6 weeks [40,41]. Clinical features include hemiparesis and visual and speech disturbances [35–37,39,43], but MRI abnormalities, such as perilesional contrast enhancement, occur in only 20–50% of evaluable reports [35–37,39–41].

Histopathological data have come largely from case series of patients with paradoxical PML IRD [25–30]. These reports describe perivascular infiltrates, with or without parenchymal infiltrates, of lymphocytic cells, typically CD8 T cells, macrophages and occasional CD20 B cells [25–30]. One report noted multinucleated giant cells in the parenchyma [25].

It is unclear whether the distinction between paradoxical PML IRD and PML that emerges after commencing HAART reflects any real underlying pathogenic difference. With respect to the pathogenesis of PML occurring after HAART initiation, Du Pasquier and Koralnik [36] noted that patients with JCV-specific CD8 T cells had greater survival than those without and went on to postulate that HAART leads to a decrease in CNS cytokines (IFN-α and IL-12), which permits the reactivation of PML [36]. This hypothesis does not explain, however, why PML develops in the setting of untreated HIV disease with high plasma and cerebrospinal fluid (CSF) HIV viral loads with which HIV-1 tat may increase JCV replication through its transactivation of the JCV late promoter in glial cells [44].

Although HAART is the cornerstone of therapy for HIV-associated PML [45–47], there is no evidence that neuro-HAART (three or more agents with superior CSF penetration) improves outcome compared with non-neuro-HAART regimens [47]. Treatment of paradoxical PML IRD with HAART alone has been associated with improvement [35,37] or deterioration [28,37,39]. Adjunctive corticosteroids may afford short-term improvement [25], general improvement [30], or no benefit at all [29]. There are few evaluable reports on specific treatment outcomes of patients with PML that emerges after commencement of HAART [35,39,42,43]; in this patient group remaining on HAART alone has been associated with death [39] or eventual improvement [35]. The addition of IFN-α [39] or corticosteroids to HAART has led to improvement in a few cases [42,43]. Recently mirtazapine has been reported to have potential benefit in HIV-uninfected patients with PML [48,49].

**Varicella zoster virus**

Varicella zoster virus (VZV) is a neurotropic human herpes virus that remains latent in the dorsal root ganglia following primary varicella zoster infection. Cutaneous VZV IRD has been reported in 8–12% of adults [9,50,51].
and in up to 11% of children [52]. In the pre-HAART era the prevalence of clinical CNS VZV disease was 0.7–7% [53,54]. There are a few reports of CNS VZV IRD, including one patient with transverse myelitis [55] and two patients with encephalitic presentations [56,57]. Both encephalitis patients had a prior history of cutaneous VZV [56,57]. Diagnosis was confirmed in all cases by a positive CSF VZV PCR. Treatment with methylprednisolone and acyclovir [55] or acyclovir alone [56,57] resulted in favourable outcomes.

The pathogenesis of CNS VZV IRD has not been fully elucidated. One case–control study of patients with cutaneous VZV IRD revealed a significantly greater increase in peripheral CD8+ cells in patients who developed zoster than controls [50]. As a corollary, a rise in CD8+ cells and natural killers cells confined to the CNS compartment was reported in the patient with VZV IRD transverse myelitis [55].

**Herpes simplex virus**

Herpes simplex viruses (HSV-1, HSV-2) are neurotropic human herpes viruses that cause oral herpes, genital herpes, and encephalitis. Both viruses are a common cause of mucocutaneous HSV IRD [5,58], but CNS HSV IRD is extremely rare, with only one reported case of presumptively diagnosed HSV CNS IRD encephalomyelitis [5].

The pathogenesis of oral and genital HSV IRD is not entirely clear although a genetic predisposition has been proposed [6,59]. HAART has been associated with a rise in IFN-γ production by HSV-specific peripheral blood mononuclear cells [60] but this finding has not yet been linked to a role in the pathogenesis of HSV IRD.

**Cytomegalovirus**

Following primary cytomegalovirus (CMV) infection, the virus remains latent, predominantly within peripheral blood monocytes [61]. CMV IRD usually involves the eyes and CNS CMV IRD is rare. In one case of presumptive CMV ventriculitis IRD that occurred 10 days after commencing HAART, the patient responded well to a combination of intravenous ganciclovir and foscarnet therapy followed by valganciclovir maintenance [62]. A second case report details a patient with CMV polyradiculopathy that developed 1 month after commencing HAART, who made a full recovery with intravenous ganciclovir treatment [63].

The pathogenesis of CNS CMV IRD is unknown but a predominance of restored CMV-specific CD8+ T cells, relative to restored CMV-specific CD4+ T cells in patients with CMV IRD retinitis has been noted, suggesting that CD8+ T cells play an immunopathogenic role [6].

**Human immunodeficiency virus**

HIV-associated dementia (HAD) occurs in approximately 15% of patients with advanced, untreated HIV disease [64,65]. In contrast, HIV CNS IRD is uncommon with fewer than a dozen cases reported in the literature [31–33] wherein pre-existing HAD was reported to worsen soon after, or develop up to 12 months after, commencement of HAART [31,33]. The outcome was poor with the notable exception of one patient who received adjunctive methylprednisolone [33]. Histopathological findings were compatible with HIV encephalitis in two reports [31,33] and included prominent perivascular lymphocytic infiltrates, predominantly comprising CD8+ cells [31,33].

**Human T lymphotropic virus type-2**

There has been one recent case report of a patient co-infected with HIV and human T lymphotropic virus (HTLV)-2 who developed a spastic paraparesis after commencing HAART [66]. Unlike HTLV-1, HTLV-2 is infrequently associated with spastic paraparesis [67]. HAART does not appear to decrease the HTLV-1 or -2 DNA proviral copy number in peripheral blood mononuclear cells [68].

**BK virus**

There has been one recent case report involving the polyoma virus, BK virus, as a cause of IRD meningoencephalitis [69]. The patient responded to a switch in his HAART regimen after cessation of empirical anti-Toxoplasma therapy, dexamethasone and acyclovir [69].

**Parvovirus B19**

Nolan et al. [70] reported a case of an HIV-positive patient with a history of chronic parvovirus B19 infection and red cell aplasia that required blood transfusions and intravenous immunoglobulin therapy. After commencing HAART the patient developed speech and focal motor deficits, associated with a rapid fall in haemoglobin level. CSF analysis and biopsy of the parietal lobe were positive for parvovirus B19. HAART was continued and intravenous immunoglobulin was added which effected improvement in his anaemia but not his neurological symptoms and HAART was, therefore, discontinued [70].

**Cryptococcus neoformans**

Cryptococcal meningitis remains the most common life-threatening fungal infection among patients with AIDS [71] and may occur as a primary presentation of HIV infection, or after initiation of HAART [cryptococcal IRD]. The incidence of CNS cryptococcal IRD ranges...
The first report of cryptococcal IRD was a case series of three patients who presented with cryptococcal meningitis following initiation of ART, one of whom had a positive cryptococcal antigen test but negative fungal cultures [71,72]. Since then the literature abounds with case reports, case series and reviews of CNS cryptococcal IRD [71, 73–80]. The definition of cryptococcal IRD is similar to previously published definitions of IRD, but requires negative fungal cultures. Cryptococcal IRD usually presents as lymph node enlargement (lymphadenitis) or CNS cryptococcal IRD [71]. CNS cryptococcal IRD may present as a meningitis syndrome or as a mass lesion (cryptococcoma) [71]. The meningitis presentation is more common, and requires differentiation from a relapse of cryptococcal meningitis due to the failure of secondary antifungal prophylaxis. Shelburne et al. [22] reported that patients with cryptococcal meningitis-related IRD had higher values for cerebrospinal fluid opening pressure, glucose levels and white blood cell counts than patients with relapsed HIV-associated cryptococcal meningitis. This differentiation may be helpful to practitioners who do not have access to reliable fungal diagnostics. Cranial imaging shows meningeal or choroid plexus enhancement or linear perivascular enhancement in the sulci [75,81].

The optimal treatment of cryptococcal CNS IRD has not been established and approaches have included no alteration of therapy [72], continued antifungal therapy [78], systemic corticosteroids [75,78,81], and thalidomide [78]. Clinical guidelines and reviews of HIV-associated cryptococcal meningitis recommend serial lumbar punctures, with or without corticosteroids [82–84]. HAART interruption is not recommended unless there is life-threatening raised intracranial pressure. Immune modulation with anticytokine therapies is being investigated.

Early reports of cryptococcal IRD described favourable outcomes [71] but more recent reports from both industrialized and developing country settings have reported significant mortality [78,80]. In a South African study, Lawn et al. [80] reported that six of nine patients with post-HAART cryptococcal meningitis died, while Lortholary et al. [78] reported one patient who died after an acute presentation. Experience from a cohort in Uganda mirrors these findings: seven of 24 cryptococcal menigitis patients who initiated ART developed IRD, four of whom died [85]. Clinical trials to determine the optimal timing of initiation of HAART and the management cryptococcal IRD are urgently required.

**Mycobacterium spp.**

The first reports of mycobacterial IRD were among HIV-infected patients on zidovudine monotherapy who presented with unusual manifestations of *Mycobacterium avium* complex (MAC) infection [7]. In contrast, IRD associated with *Mycobacterium tuberculosis* was not reported until the HAART era with the majority of patients presenting with worsening pulmonary symptoms or lymphadenitis [7]. This may have been a result of underreporting, as paradoxical reactions are a well recognized complication of tuberculosis treatment [86].

The first case of CNS IRD due to *M. tuberculosis* was a patient with miliary tuberculosis who developed intracranial tuberculomas [87]. The second was a patient with a tuberculous brain abscess who developed a clinical and radiological deterioration 1 month after commencing HAART [69]. In a larger study [88], paradoxical reactions were more common in HIV-infected than -uninfected patients (28% versus 10%) with tuberculosis and two cases of CNS paradoxical reactions reported.

Recently two further cases of CNS IRD associated with tuberculomas have been reported [89,90]. The first was an HIV patient from Guinea who presented with a meningeval syndrome 1 month after starting HAART. After initial response to antituberculous therapy, corticosteroids and HAART interruption he deteriorated with headache, homonymous hemianopsia and cranial MRI showed multiple tuberculomas. This case is unusual in that it describes the unmasking form of IRD closely followed by a paradoxical reaction [89]. The second report [90] was of a Chinese patient who presented with pulmonary TB, CNS symptoms, and multiple ring-enhancing lesions on cranial MRI. He responded to treatment with antituberculous therapy, prednisolone and HAART but cranial MRI showed resolution of some lesions, enlargement of others and development of new lesions. Although the development of tuberculomas during treatment is believed to be rare, a recent study of the radiological features of tuberculous meningitis in 43 HIV-negative patients [91] demonstrated that tuberculomas develop in 77% of patients during the course of therapy. This situation raises the question of whether asymptomatic radiological deterioration should be used as a diagnostic criterion for CNS IRD due to *M. tuberculosis*. In an ongoing randomized controlled trial of immediate versus deferred HAART for HIV-associated tuberculous meningitis, neurological deterioration commonly occurs during the first 3 months of treatment, and is frequently accompanied by radiological deterioration (Fig. 1).
The baseline images of the (a) medulla oblongata, (c) pons and (e) mid brain are normal. The follow-up images, taken 35 days later, after highly active antiretroviral therapy initiation, show diffuse pial enhancement over (b) the medullary surface, as well as ependymal enhancement in the fourth ventricle; (d) the surface of the pons, as well as the cisternal portions of the trigeminal nerves bilaterally; and (f) the surface of the optic chiasm and optic tracts, as well as enhancing focal pial nodules in other areas including the right sylvian fissure and the inter-peduncular cistern.
Management

The management of CNS IRD is challenging as the clinical presentations are heterogeneous, the immunopathogenesis is poorly understood, and there are no randomized, controlled trial data to guide therapy. It is important to consider CNS IRD in the differential diagnosis of any patient who presents with new or worsening CNS symptoms after initiation of HAART. It is also essential to exclude other potential causes for the deterioration, but this may be difficult in resource-constrained settings.

Currently, it is not known whether to stop or continue HAART in a patient presenting with CNS IRD. On the one hand, HAART-induced immune restoration may have precipitated the neurological deterioration and stopping HAART may, therefore, result in improvement; there is no guarantee, however, that the condition will not recur when HAART is restarted. Conversely, stopping HAART increases the risk of opportunistic infections and HIV disease progression. On balance, Riedel and colleagues [11] recommend the continuation of HAART. As the risk of IRD is known to be increased in patients with a newly diagnosed opportunistic infection, a key issue is to determine the optimal time to start ART in patients presenting with a CNS opportunistic infection. Clinical trials to answer this question are ongoing.

The second therapeutic dilemma is whether to give corticosteroids. There is limited evidence supporting the use of systemic corticosteroids in individual cases of CNS IRD [7,25,29,30,33,55,78,92] but clinical trial data are lacking. Corticosteroids may be beneficial in patients with life-threatening raised intracranial pressure. There are concerns that they may be detrimental in patients who are already severely immunosuppressed, particularly if there is an underlying, untreated infection. Corticosteroids, however, have been safely used in patients with advanced HIV infection [93] and in HIV-infected patients with tuberculous meningitis [94]. Thus in patients with severe life-threatening CNS IRD systemic corticosteroids may be warranted [92]. Clinical trials to answer this important question are urgently required.

In summary, the current management of CNS IRD is not evidence-based. A more rational approach to treatment may become possible once the immunopathogenesis of IRD is better understood enabling the development of specific immunomodulatory therapies.

Conclusions

CNS IRD is becoming increasingly recognized as a complication of HAART. Diagnosis is difficult as the clinical presentation is highly variable and no simple diagnostic test exists. Differentiation of CNS IRD from other causes of neurological deterioration may be difficult, particularly in resource-limited settings. The immunopathogenesis of CNS IRD is poorly understood, although CNS infiltration of CD8+ T cells seems to be important, particularly in CNS IRD caused by viral pathogens. The management of this condition is controversial as no specific treatment exists and clinical trial data to support existing interventions are lacking. The outcome of CNS IRD is generally poor and considerable opportunities and challenges remain in the prevention, diagnosis and management of this condition.

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References

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 527).