

Unmasking Immune Reconstitution Inflammatory Syndrome (IRIS)

A report of five cases and review of the literature

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إظهار متلازمة إعادة التكوين الالتهابي (الآيريس) تقرير عن خمس حالات ومراجعة

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الملخص: تتميز متلازمة إعادة التكوين الالتهابي (آيريس) عند المرضى المصابين بمتلازمة نقص المناعة المكتسب (الايدز) بأعراض غير طبيعية بسبب الجراثيم الانتهازية. تحدث هذه عند المرضى الذين يظهرون تحسنا في عدد خلايا (سي دي 4) بعد تلقي العلاج الفعال للغاية، المضاد للفيروس القهقري. على الرغم من المعرفة الجيدة لهذه المتلازمة لا يزال هناك تحديات في التشخيص والعلاج. نعرض هنا تقرير خمس حالات لهذه المتلازمة وبأعراض متنوعة حسب الجراثيم المسببة للعدوى. ونورد أيضا مراجعة للأدبيات المنشورة حول هذه المتلازمة.

مفتاح الكلمات: فيروس نقص المناعة البشرية، متلازمة نقص المناعة المكتسب، متلازمة إعادة التكوين الالتهابي، آيريس، السل، السل غير النمطي، المستخفية، داء المقوسات، خفية الأبواغ، تقرير حالة، عُمان.

ABSTRACT: Immune reconstitution inflammatory syndromes (IRIS) in patients with acquired immune deficiency syndrome (AIDS) are characterised by atypical manifestations of opportunistic pathogens. These occur in patients experiencing improvement in CD4 cell counts following receipt of highly active anti-retroviral therapy (HAART). Although well established as a syndrome, IRIS still presents challenges in diagnosis and management. We report five cases of IRIS with diverse clinical presentations and due to different infectious aetiologies. A review of the published literature on this syndrome is also included.

Keywords: HIV; AIDS; HAART; Immune reconstitution inflammatory syndrome; IRIS; TB; Atypical mycobacterium; Cryptococcus; Toxoplasmosis; Cryptosporidium; Case report; Oman

THE INTRODUCTION OF HIGHLY ACTIVE anti-retroviral therapy (HAART) has markedly decreased the rates of opportunistic infections, the progression to AIDS, and the overall mortality for HIV-infected patients.¹ In some patients, however, the effective immune reconstitution that follows HAART can result in an exuberant inflammatory response leading to paradoxical clinical deterioration. The presence of IRIS does not mean that HAART has failed. In fact it shows that the treatment is effective.

In this report, we describe five patients at Sultan Qaboos University Hospital, Oman, who developed IRIS shortly after the initiation of HAART. In addition, a literature review on the epidemiology, aetiology, risk factors, pathogenesis, diagnosis and management of infection-related IRIS is also included in this report.

Case One

A 23 year-old male was diagnosed in 2002 with HIV-1 infection when he presented with *Cryptococcus neoformans* meningitis. At diagnosis, his CD4 count was 58cells/mm³ and the HIV-1 viral load 110,000 ribonucleic acid (RNA) copies/ml. He received amphotericin B 1mg/kg intravenously (IV) daily for the first 2 weeks, then fluconazole 400 mg PO (*per os*, i.e. orally) daily for 8 weeks followed by maintenance therapy. Cotrimoxazole was started for pneumocystis pneumonia (PCP) prophylaxis. HAART (zidovudine, lamivudine, indinavir) was started in March 2003, but was later stopped due to poor compliance. In January 2007, he was again restarted on HAART (zidovudine, lamivudine, lopinavir/ritonavir). His pre-HAART CD4 count was 35cells/mm³ and HIV-1 viral load was 159,000

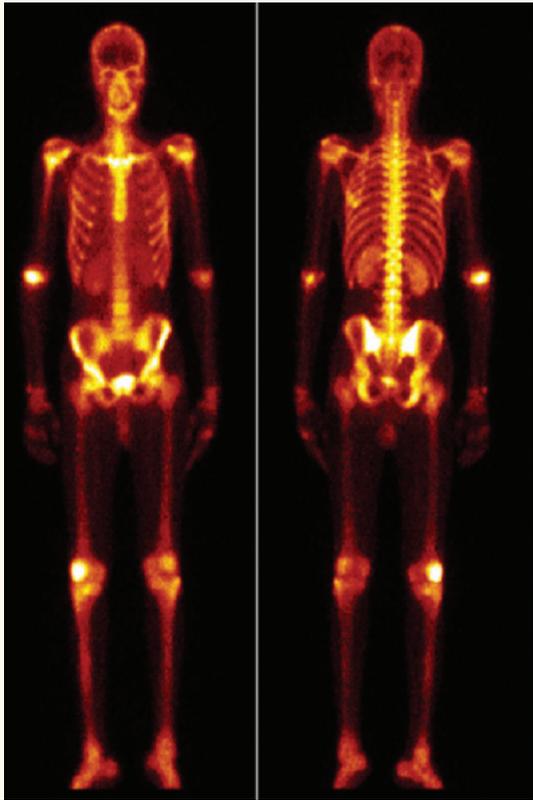


Figure 1: Three -phase bone scintigraphy delayed images show increased radiotracer uptake in right elbow and knee.

revealed swollen, warm and tender right elbow and right knee with effusion and severe restriction of movements. A whole body bone scintigraphy, using technetium-99m-methylene diphosphonate (Tc99m-MDP), was done as well as a magnetic resonance imaging (MRI) scan of the right elbow and knee joints [Figures 1 and 2, respectively].

Multifocal septic arthritis of the right elbow and knee joints with osteomyelitis was diagnosed. The right elbow and knee joints were aspirated and drained thick greenish pus. A Ziehl-Neelsen stain of the aspirate from both sites showed sheets of acid fast bacilli. The patient underwent drainage and debridement of the affected bones; tissues were also sent for mycobacterium and fungal culture. Standard quadruple antituberculous therapy (ATT) and clarithromycin were started while awaiting the culture results. HAART was continued and non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed.

A repeat CD4 count at this presentation showed it had risen to 185 cells/mm³ and HIV-1 viral load had dropped to 3350 RNA copies/ml. The culture of the aspirate of both joints and the humeral and femoral bone biopsy revealed growth of non *Mycobacterium avium* complex (non-MAC), non-tuberculous *Mycobacterium* which could not be further identified in the public health laboratory. The isolate was sensitive only to

RNA copies/ml. Seven weeks later, he presented with fever and progressive pain and swelling of the right elbow and knee joints. Clinical examination



Figure 2a: MRI Right elbow (STIR sequence in coronal plane) demonstrates bone marrow oedema in the lateral epicondyle associated with joint effusion and soft tissue swelling.



Figure 2b: Magnetic resonance image of right knee T1W FS CE in the sagittal plane showing intra osseous abscesses in condyles (not in picture) and patella with joint effusion, synovitis and bone marrow oedema.

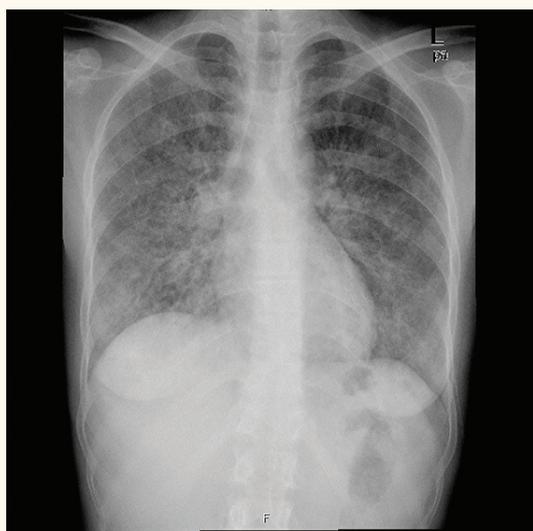


Figure 3: Frontal radiograph chest showing bilateral reticular opacities mainly in mid and lower lungs.

ciprofloxacin and clarithromycin while resistant to all standard antitubercular (ATT) drugs including rifampicin, ethambutol and aminoglycosides. The ATT treatment was stopped while ciprofloxacin and clarithromycin were continued in addition to HAART. The patient made a full recovery and has remained asymptomatic to date.

Case Two

A 38 year-old woman was diagnosed in December 2006 with HIV-1 infection after presenting with *Pneumocystis jirovecii* pneumonia (PCP) [Figure 3]. She had a CD4 count of 8 cells/mm³ and the HIV-1 viral load of 314,000 RNA copies/ml at diagnosis. Three weeks later she was started on HAART (zidovudine, lamivudine and efavirenz). About four weeks after commencing HAART, she developed fever, headache and vomiting. The clinical examination showed neck stiffness and positive Kernig's sign. The computed tomography (CT) scan of the brain was normal. A lumbar puncture was performed and the subsequent India ink stain and *Cryptococcus* antigen were both positive in the cerebrospinal fluid (CSF). *Cryptococcus neoformans* was later isolated from the CSF. The patient received liposomal amphotericin 5mg/kg IV daily for 2 weeks followed by fluconazole 400 mg PO daily for 8 weeks and later maintained on oral fluconazole 200 mg daily. HAART was discontinued temporarily during the initial phase of treatment

(the first two weeks), but was later restarted. At this presentation, the CD4 count was 35cells/mm³ and the HIV-1 viral load was 35,000 RNA copies/ml. The patient had a full recovery with follow-up CSF cultures documenting sterility.

Case Three

A 57 year-old man was diagnosed in August 2006 with HIV-1 infection when he presented with biopsy proven *Toxoplasma gondii* brain abscesses. The CD4 count at presentation was 85cells/mm³ and the HIV-1 viral load was >750,000 RNA copies/ml. He was treated with a combination of pyrimethamine 75 mg PO daily, sulfadiazine 1g PO 6 hourly and folinic acid 15 mg PO daily for 6 weeks. He was afterwards put on maintenance therapy. The patient's symptoms improved as a result of this treatment. A follow up MRI brain confirmed resolution of the lesions. HAART (zidovudine, lamivudine, abacavir) was then started. Eight weeks later, he presented with fever, abdominal pain and diarrhoea. The clinical examination revealed jaundice and tenderness at the right upper quadrant of the abdomen. Acute cholangitis was suspected. An MRI scan of the abdomen was done [Figure 4] and revealed dilated intrahepatic biliary ducts with the contrast uptake suggesting inflammation.

The patient underwent upper gastrointestinal (GI) endoscopy, which showed an ulcerative necrotic lesion and areas of hyperaemia involving

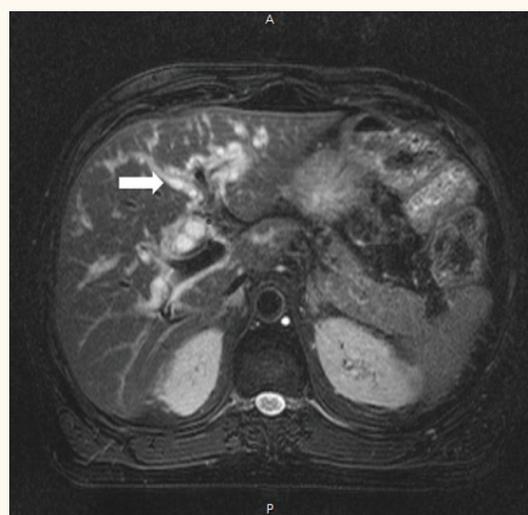


Figure 4: Magnetic resonance imaging scan of the abdomen - T2W FS in the axial plane - reveals dilated intra hepatic bile ducts with signs of cholangitis.

the entire duodenum. A duodenal aspirate and biopsy showed the presence of *Cryptosporidium*. The stool was also positive for *Cryptosporidium*. The test for cytomegalovirus by polymerase chain reaction (CMV-PCR) was negative. The CD4 count at this presentation was 287 cells/mm³ and the HIV-1 viral load was 4670 RNA copies/ml. The patient was started on paromomycin 500 mg PO three times daily and azithromycin 500 mg PO once daily. The HAART was continued and a complete resolution of the symptoms was achieved. A follow-up upper GI endoscopy and MRI six weeks later were both normal.

Case Four

A 30 year-old woman was diagnosed in 2003 with HIV-1 infection during pregnancy. The CD4 count was 20 cells/mm³ and the HIV-1 viral load was >750,000 RNA copies/ml. She was then lost to follow-up. In 2005, she presented with severe CMV and *Candida esophagitis* (diagnosis made by upper GI endoscopy and oesophageal biopsy). She was treated with fluconazole 400 mg intravenously (IV) daily and ganciclovir 5mg/kg IV twice daily. Pentamidine 300 mg via aerosol once monthly was also started for prophylaxis against PCP as the patient had a severe allergy to sulpha. HAART (zidovudine, lamivudine, indinavir) was started. Three weeks later, the patient presented with generalised tonic-clonic seizures. The clinical

examination was normal. An urgent MRI brain scan [Figure 5a & b] was consistent with cerebral toxoplasmosis.

The serology for toxoplasmosis was positive in both immunoglobulin G and M (IgG & IgM). A working diagnosis of cerebral toxoplasmosis was made and the patient was started on combination of pyrimethamine 75 mg PO daily, clindamycin 450 mg PO three times daily and folinic acid 15 mg PO daily for 6 weeks and later was put on maintenance therapy.

The HAART was discontinued temporarily. The CD4 count at this presentation had risen to 84 cells/mm³ and HIV-1 viral load had fallen to 7130 RNA copies/ml. The patient remained asymptomatic during this period with no recurrence of convulsions. A follow-up MRI brain scan at the end of 6 weeks of treatment confirmed complete resolution. The same HAART regimen was then resumed with no unwanted consequences.

Case Five

A 23 year-old man was diagnosed in October 2005 with HIV-1 infection when he presented with uncomplicated *Salmonella* bacteraemia. The CD4 count was 10 cells/mm³ and the HIV-1 viral load was >750,000 RNA copies/ml. The US Centers for Disease Control and Prevention (CDC) stage at diagnosis was B3. He received ciprofloxacin 400 mg IV twice daily for two weeks. HAART

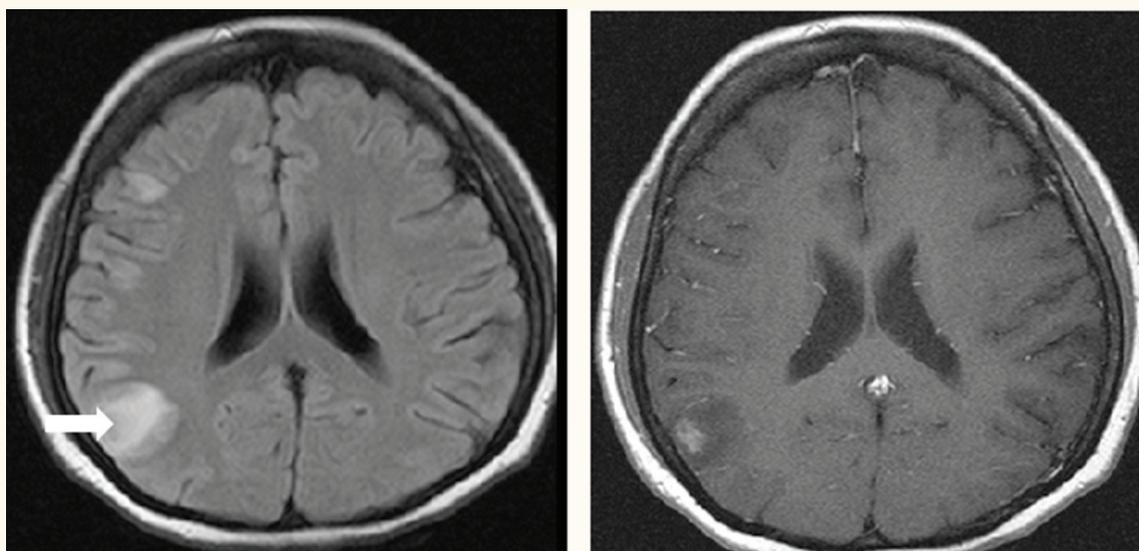


Figure 5A & 5B: MRI Brain FLAIR and T1W CE sequences showing enhancing lesion with perilesional oedema in right parietal lobe.

Table 1: Table summarising the CD4 counts of the five patients before and after initiation of HAART and the clinical manifestation of IRIS

Case Number	CD4 Count (cells/mm ³) at initiation of HAART	Viral load (RNA copies/ml) at initiation of HAART	CD4 count (cells/mm ³) at time of IRIS	Viral load (RNA copies/ml) at time of IRIS	Clinical disease characterising IRIS	Time to IRIS (week)	Antiretroviral regimen	Outcome
1	35	159,000	185	3350	Non tuberculous mycobacterial infection (not specified) of bone and joint	7	Zidovudine, Lamivudine & Lopinavir/Ritonavir.	Cured
2	8	314,000	35	35,000	Cryptococcal meningitis	4	Zidovudine, Lamivudine & Efavirenz	Cured
3	85	>750,000	287	4670	Cryptosporidial cholangitis	8	Zidovudine, Lamivudine & Abacavir	Cured
4	20	>750,000	84	7130	Toxoplasmosis	3	Zidovudine, Lamivudine & Indinavir	Cured
5	10	>750,000	32	160,000	Tuberculous lymphadenitis	4	Abacavir, Lamivudine & Efavirenz	Cured*

Note: *Patient died later from advanced metastatic Kaposi sarcoma

Legend: HAART = highly active anti-retroviral therapy; IRIS = immune reconstitution inflammatory syndrome; RNA = ribonucleic acid.

(abacavir, lamivudine, efavirenz) was commenced. Cotrimoxazole was started for primary prophylaxis for PCP. Four weeks after the initiation of HAART, he developed fever with left-sided, enlarged, painful cervical lymph-nodes. Clinical examination showed multiple left-sided tender cervical lymph-nodes, the largest measuring 3 × 4 cm. Both liver and spleen were enlarged.

The tuberculin skin test (TST) was non-reactive. The cervical lymph-node biopsy showed sheets of acid-fast bacilli. Standard quadruple ATT was commenced and the HAART suspended during the initiation phase of ATT; NSAIDs were added. The CD4 count at this presentation had risen to 32 cells/mm³ and the HIV-1 viral load had fallen to 160,000 RNA copies/ml. A culture of the lymph-node grew fully sensitive *Mycobacterium tuberculosis*. The ATT was continued and the same HAART regimen (but with the dose of efavirenz increased to 800 mg daily) was reintroduced after completion of the initiation phase of ATT. There were no undue side effects. Full recovery was achieved with resolution of the lymphadenopathy and regression of the hepatosplenomegaly.

Discussion

We described five patients with advanced HIV-1 infection in whom initiation of HAART have resulted in unmasking of an underlying occult opportunistic infection. The five cases have all the classical features suggestive of immune reconstitution inflammatory syndrome (IRIS). All five had advanced HIV disease with a very high viral load and low CD4 count at the initiation of the therapy (HAART). The paradoxical worsening and the presentation, with an opportunistic infection 2–8 weeks after the initiation of HAART in all five cases, correlated with the drop in viral load and the rise in CD4 count. The variety of pathology in these five cases associated with IRIS is also remarkable and is consistent with the common rule of IRIS that ‘anything is possible’.

The HAART for HIV infection has been one of the most dramatic progressions in the history of medicine. Since its introduction, HAART has led to significant declines in AIDS-associated morbidity and mortality.² These benefits are, in part, a result of partial recovery of the immune system, manifested by increases in CD4+ T-lymphocyte counts and decreases in plasma HIV-1 viral loads.³

Soon after the introduction of HAART,

clinicians noticed that some patients initiating HAART experienced unique symptoms during immune system recovery. In these patients, clinical deterioration occurs despite increased CD4+ T lymphocyte counts and decreased plasma HIV-1 viral loads.⁴ This clinical deterioration is a result of an inflammatory response of the immune system to both intact subclinical pathogens and residual antigens. Because clinical deterioration occurs during immune recovery, this phenomenon has been described as immune restoration disease (IRD), immune reconstitution syndrome (IRS), and paradoxical reactions. Given the role of the host inflammatory response in this syndrome, the term immune reconstitution inflammatory syndrome (IRIS) has been proposed.⁵

IRIS can be defined as a pathological inflammatory response and paradoxical clinical deterioration as a result of HAART related immune recovery or reconstitution in HIV infected persons. In other words, IRIS is a syndrome that occurs because a patient develops an exuberant response to appropriate therapy. IRIS is now a widely recognised phenomenon that can complicate HAART.^{6,7,8}

How IRIS develops is not yet well understood and its pathogenesis remains largely speculative. Current theories concerning the pathogenesis of the syndrome involve a combination of underlying antigenic burden, the degree of immune restoration following HAART, and host genetic susceptibility. These pathogenic mechanisms may interact and likely depend on the underlying burden of infectious or non-infectious agents.

As illustrated in all the five cases above, the majority of patients who develop IRIS do so within the first 4 to 8 weeks after starting HAART. However, the interval between the start of HAART and the onset of IRIS is highly variable, ranging from less than 1 week to several months after HAART initiation.⁹ Furthermore, most patients who develop IRIS have had high viral loads and very low CD4+ T-lymphocyte (CD4+) counts. In this report, all five patients had CD4 counts of <100 cells/mm³ at the start of HAART. In addition, three patients had an HIV-1 viral load of >750,000 RNA copies/ml.

The frequency of IRIS has not been reported conclusively and the overall incidence of the syndrome itself remains largely unknown, being dependent on the population studied and its underlying opportunistic infections burden. In the

largest study of IRIS to-date, 31.6% of HIV infected patients developed IRIS while on HAART.¹⁰ In a large retrospective analysis examining all forms of IRIS, 25% of patients exhibited one or more disease episodes after initiation of HAART.⁴ Other cohort analyses examining all manifestations of IRIS estimate that 17–23% of patients initiating HAART will develop the syndrome.^{11,12} Another study demonstrated that up to one third of patients with HIV/tuberculosis co-infection who begin HAART in resource-limited countries could be at risk of developing tuberculosis-associated IRIS (also known as TB-IRIS).¹³

Collation of the clinical, immunological and immune-genetic data presented over the last 15 years has identified risk factors for IRIS.⁴ A higher viral load and low CD4 T cell count at the start of HAART along with a rapid drop in viral load with treatment, as shown in all five cases in this report, has been found to be a favourable setting for IRIS to occur. In the affected patients, CD4 T cell counts are often <50 cells/mm³ at the start of HAART and subsequently increase more than 2–4 fold during the 12 months after initiation of HAART, and a significant decrease in HIV load of more than 2 log₁₀ copies/ml is often noted.¹⁴

IRIS manifestations are diverse and depend on the infectious or non-infectious agent involved. These manifestations have not been precisely defined. In general, and as illustrated in the case reports above, they are characterised by fever and worsening of the clinical manifestations of the underlying opportunistic infection. These clinical manifestations may be at the site of a previously recognised opportunistic disease (none of our patients) or may “unmask” disease at new sites not previously known to be infected by the pathogen (none of our patients). They may also represent a response to a previously unrecognised additional pathogen (all five patients reported here). A paradoxical clinical worsening of a known condition or the appearance of a new condition after initiating therapy characterises the syndrome.

Mycobacterium tuberculosis (TB) is among the most frequently reported pathogens associated with IRIS. The commonest clinical manifestations of TB-IRIS are fever, lymphadenopathy and worsening respiratory symptoms.¹³ In most studies, TB-IRIS occurs within two months of HAART initiation. These studies suggest that the onset of

Mycobacterium-associated IRIS is relatively soon after initiation of HAART, and clinicians should maintain a high level of vigilance during this period.

The last patient in our report (Case Five) was a classic case of TB-IRIS. He presented with fever and cervical lymph-nodes enlargement shortly (four weeks) after initiation of HAART. Hepatosplenomegaly probably signifies widespread TB disease and its subsequent regression on ATT further supports this hypothesis.

In addition to *Mycobacterium tuberculosis*, nontuberculous mycobacteria are also frequently reported as causative pathogens in IRIS. *Mycobacterium avium complex* (MAC) remains the most frequently reported atypical mycobacterium linked with IRIS. Other atypical mycobacteria are rarely associated with IRIS.

The first patient in our series (Case One) had a nontuberculous *Mycobacterium* that was not MAC (and could not be further identified) which resulted in a severe form of multiple-site osteomyelitis. This disease manifested shortly after introduction of HAART (seven weeks later). Furthermore, it occurred at the time of marked immune recovery and marked improvement in CD4 count (CD4 count had risen 4 to 5 fold by then).

Soon after the introduction of HAART, it was observed that some patients presented with an initial or recurrent episode of cryptococcal meningitis during the first few weeks of therapy;¹⁵ however, IRIS with cryptococcal meningitis is rare.^{16,17} The most common IRIS syndrome associated with cryptococcal infection is lymphadenitis.

IRIS was reported in 30–33% of HIV-infected patients with *Cryptococcus neoformans* after the initiation of HAART.¹⁸ Lower CD4-cell count and higher HIV-RNA concentrations at the onset of infection correlated with a higher risk of IRIS.¹⁸ Patients with IRIS also had a greater reduction in HIV-RNA concentration within 90 days of HAART initiation,¹⁹ and had a greater fungal burden at the onset of infection.¹⁸ Furthermore, initiation of HAART within 30–60 days of the treatment of fungal infection has been associated with a higher risk of IRIS.²⁰

The second patient (Case Two) in our report presented with an initial, first episode of cryptococcal meningitis while on HAART (3 weeks later). She had an extremely low CD4 count at the time of the initiation of HAART (CD4 8 cells/mm3)

and had a dramatic immune recovery with a 4-fold CD4 count rise and >1 log reduction in the HIV-1 viral load at time of presentation.

The number of reports of IRIS associated with parasitic diseases is small but increasing. Only two cases of suspected IRIS associated with toxoplasma encephalitis have been reported in published literature. In one case, no clinical details were given.¹² In the other, an HIV-infected patient with a nadir CD4 cell count of 83 cells/mm3 presented with a focal seizure after 3 weeks of HAART.²¹

The fourth patient in this report (Case Four) presents, to our knowledge, only the third reported case in the literature of IRIS associated with toxoplasma encephalitis. This patient presented with generalised seizures three weeks after initiation of HAART. He had an exceptionally low CD4 count (CD4 count 2 years earlier was 20cells/mm3) and a very high HIV-1 viral load (>750,000 RNA copies/ml) at the time of initiation of HAART. He had a dramatic immune recovery with a 4-fold CD4 count rise and major reduction in the HIV-1 viral load of > 2 log reduction at the time of presentation with cerebral toxoplasmosis. The diagnosis of cerebral toxoplasmosis was made on the basis of positive serology, multiple ring-enhancing intra-cerebral lesions on an MRI scan and a positive response to treatment for toxoplasmosis with complete resolution on follow-up brain imaging.

Of interest is that there are no frequent reports in the published literature of IRIS associated with *Cryptosporidium* infection. We here report a rare case of *Cryptosporidium* infection associated with IRIS.

Our patient (Case Three) presented eight weeks following initiation of HAART with fever, abdominal pain and diarrhoea. This occurred at a time where immune recovery was dramatic (CD4 count rise from 85 to 287 cells/mm3) and HIV-1 viral load reduction was substantial (HIV-1 viral load reduction > 2 log). Endoscopy proven extensive duodenal inflammation and ulcerations were found in addition to clinical, biochemical, and an MRI assisted diagnosis of cholangitis. Furthermore, the duodenal aspirate and multiple duodenal biopsies confirmed the presence of *Cryptosporidium*. The stool sample was also positive for *Cryptosporidium*. No other aetiologies were identified. The resolution of symptoms and normal subsequent endoscopy further supports the diagnosis of IRIS associated

Cryptosporidium. To our knowledge this is the first reported case in the literature.

Diagnosis of IRIS is clinically challenging and involves differentiation between the progression of the initial opportunistic infection (OI) (including the possibility of antimicrobial resistance and treatment failure); development of a new OI; unrelated organ dysfunction, or drug toxicity. IRIS should be suspected in patients who show clinical or radiologic deterioration following initiation of HAART accompanied with improvement in CD4 count and viral load.

Since there is no diagnostic test for IRIS, confirmation of the disease relies heavily upon case definitions incorporating clinical and laboratory data. French *et al.*⁷ and Shelburne *et al.*²² published two of the most widely used IRIS case definitions in the literature. In a recent article, published in the *Clinical Infectious Diseases* journal, Haddow *et al.* proposed a revised case definition of IRIS incorporating both definitions along with separate definitions for unmasking and paradoxical IRIS.²³ The current management of IRIS remains controversial and therapy for IRIS is largely empiric. There are no well-controlled trials concerning the management of IRIS. All evidence in the literature regarding the management of IRIS is found in case reports and small case series reporting on management practice. Furthermore, no clear guidelines exist regarding the continuation of HAART during IRIS; therefore, the decision to continue HAART in spite of IRIS should be based on the clinical scenario. If the pathogens involved in IRIS are not amenable to specific treatment, or if life-threatening events occur and steroids are ineffective, one should consider suspending antiretroviral therapy.²⁴

Symptomatic therapy for IRIS can be tried with NSAIDs and steroids. Immune modulation in some instances is warranted, but specific drugs and protocols are lacking. Other modalities tried include thalidomide and intravenous immunoglobulin (IVIG)

In our report, HAART was discontinued temporarily in three patients (cases Two, Four and Five). These patients had cryptococcal meningitis, cerebral toxoplasmosis and TB lymphadenitis respectively. HAART was discontinued in the patient with cryptococcal meningitis during the induction phase of treatment (first two weeks) and

was restarted thereafter with no complications. In the patient with cerebral toxoplasmosis, HAART was suspended until complete resolution of the brain abscesses and associated oedema (six weeks). HAART was then reintroduced with no problems. In both scenarios, HAART was suspended temporarily to minimise the inflammatory process and its potential unwanted consequences in a critical site (brain). In the patient with TB-IRIS, HAART was suspended during the initiation phase of ATT (first two months) only to enhance patient compliance with TB treatment. Both HAART and ATT were later combined resulting in cure.

HAART was continued without interruption in the remaining two patients (cases One and Three). In the patient with atypical *Mycobacterium* associated-osteomyelitis (Case One), in addition to continuing HAART, NSAIDs were used. Specific therapy with clarithromycin and moxifloxacin resulted in cure. In the patient with *Cryptosporidium* induced duodenitis and cholangitis (Case Three), HAART was continued and specific prolonged treatment with paromomycin and azithromycin was given resulting in clearance of the parasitic infection and subsequent cure.

Although some IRIS cases are short-lived, or cause minor clinical problems, others may result in significant morbidity and sometimes death. However, IRIS does not appear to have favourable or unfavourable implications about patient survival, with the possible exception of IRIS associated with cryptococcal meningitis.¹⁰

To date, with exception of the patient with TB-IRIS (Case Five), who died from disseminated Kaposi sarcoma, the other four patients have remained well and had optimal clinical, immunologic and virological responses on HAART.

Conclusion

Our cases establish the fact that IRIS is a significant problem in the post HAART era and is associated with several challenges for the treating physicians. As the use of HAART increases around the world (including developing countries where a large number of severely immune-deficient patients are being given HAART), physicians managing patients with HIV infection will encounter increasing numbers of patients with IRIS. The inclusion of IRIS in the differential diagnosis of a patient who

presents with an inflammatory process after initiating HAART allows for a focused approach to diagnosis and therapy. Further studies are needed to help us to understand how to deal with this clinically significant problem. Guidelines for the management of IRIS and the use of HAART during IRIS also need to be developed.

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