

ORIGINAL RESEARCH

Impact of highly active antiretroviral therapy on organ-specific manifestations of HIV-1 infection

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In the last 10 years, interesting results have been reported concerning the impact of highly active antiretroviral therapy (HAART) on the changing pattern of organ-specific manifestations of HIV-1 infection. There has been a clear step-wise reduction in the incidence of several opportunistic infections (OIs), particularly *Pneumocystis carinii* pneumonia, whereas a nonsignificant reduction in incidence has been observed for other organ-specific diseases, including invasive cervical cancer and Hodgkin disease. In addition, several organ-specific manifestations, including HIV-associated nephropathy, wasting syndrome and cardiomiopathy, are a direct consequence of damage by HIV-1, and so HAART may have a therapeutic effect in improving or preventing these manifestations. Finally, the introduction of HAART has seen the emergence of several complications, termed immune reconstitution inflammatory syndrome, which includes OIs such as cytomegalovirus vitritis, *Mycobacterium avium* complex lymphadenitis, paradoxical responses to treatment for tuberculosis, and exacerbation of cryptococcosis. Because not all HIV-1 organ-specific manifestations are decreasing in the HAART era, this review will analyse the influence of HAART on several organ-specific manifestations, and in particular OIs related to several organs, cerebral disorders and HIV-1-related neoplasia.

Keywords: HAART, HIV infection, organ manifestations, AIDS

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Introduction

The natural history of HIV-1 infection has changed in the era of highly active antiretroviral therapy (HAART), with the incidence of opportunistic infections (OIs) associated with HIV-1 infection and AIDS-related deaths having significantly decreased [1,2]. However, the decline in the incidence of AIDS-defining illnesses has not been paralleled by a change in the spectrum or frequency of AIDS-defining illnesses [3]. Nevertheless, the percentage of hospitalized HIV-1-infected patients who have OIs has remained stable in the HAART era [4], and OIs seem to appear with the same frequency as in the pre-HAART era.

Organ-specific manifestations in the pre-HAART era

The clinical manifestations of HIV-1 disease affect multiple organ systems. The severity of each manifestation varies by organ system and can be related to HIV-1 replication in infected tissue, concomitant OI of the organ, or an adverse end-organ drug effect.

Before the introduction of HAART at the end of 1996, the clinical spectrum of AIDS was wide, and practically all organs were involved during the HIV-1 infection. The most common organ-specific manifestations in HIV-1-infected patients included AIDS-defining illnesses of the lung (*Pneumocystis carinii* pneumonia), brain (*Toxoplasma* encephalitis and HIV-1 encephalitis), heart (pericarditis), gut [candidal and cytomegalovirus (CMV) infection, and oesophagitis], kidney (focal glomerulosclerosis), skin (Kaposi's sarcoma), and lymphoid tissue (non-Hodgkin lymphoma) (Tables 1, 2 and 3).

In addition, several AIDS-defining illnesses were predictors of poorer survival in the pre-HAART era, such as CMV disease, HIV-1 encephalopathy and *Toxoplasma* encephalitis.

Organ-specific manifestations in the HAART era

The impact of HAART on the changing pattern of HIV-1 organ-specific manifestations led to unequivocal contrastant results [3,5,6]. There was a clear step-wise reduction in

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Table 1 Organ-specific manifestations in the pre-HAART era

	Organ-specific manifestations	
Organ	**High frequency**	**Moderate or low frequency**
Lung	PCP	Bacterial pneumonia CMV pneumonia Mycobacterial infection
Brain	*Toxoplasma* encephalitis HIV-1 encephalitis	HIV-1 encephalitis CMV infection Progressive multiple leukoencephalopathy
Heart	Pericarditis	Focal myocarditis Pulmonary hypertension
Kidney	Focal glomerulosclerosis (HIVAN)	Membrane and proliferative glomerulonephritis Minimal-change glomerulonephritis
Gut	Candidal and CMV oesophagitis	Enterocolitis (CMV, *Cryptosporidium* spp. and *Salmonella* spp.)
Liver	Mycobacterial hepatitis	CMV hepatitis Drug-induced hepatitis Non-Hodgkin lymphoma
Oral cavity and skin	Oral candidiasis Seborrheic dermatitis	Bacterial cutaneous infections Molluscum contagiousum Psoriasis Atopic dermatitis
Eye	Retinal microvasculopathy	CMV retinitis *Toxoplasma* retinochoroiditis
Cutaneous and mucosal system, and lymph nodes	Kaposi's sarcoma Non-Hodgkin lymphoma Hodgkin disease	Multicentric Castleman's disease Body cavity lymphoma

CMV, cytomegalovirus; PCP, *Pneumocystis carinii* pneumonia.

Table 2 Changing pattern of AIDS-defining illnesses with HAART: review of published studies

Authors	No. of patients	Decrease of incidence	Persistence or significant increase of incidence
Forrest *et al.*, 1998 [3]	2533	Candidal infection, CMV disease, MAC infection, AIDS dementia complex, PCP, Kaposi's sarcoma	
Ives *et al.*, 2001 [5]	1538	PCP, Kaposi's sarcoma, criptosporidiosis	Oesophageal candidiasis, MAC infection
Detels *et al.*, 2001 [9]*	2013	MAC infection, CMV disease, oesophageal candidiasis, PCP	
Dore *et al.*, 2002 [10]	4351	MAC infection, CMV disease, cryptosporidiosis, Kaposi's sarcoma	Tuberculosis, oesophageal candidiasis, non-Hodgkin lymphoma, AIDS dementia complex
Ledergerber *et al.*, 1999 [11]	2410	PCP, toxoplasmosis, Kaposi's sarcoma	Oesophageal candidiasis, MAC infection, CMV disease, non-Hodgkin lymphoma

*In this study the investigators only evaluated the most common opportunistic infections. CMV, cytomegalovirus; PCP, *Pneumocystis carinii* pneumonia; MAC, *Mycobacterium avium* complex.

the incidence of several OIs, particularly *Pneumocystis carinii* pneumonia (PCP), while a nonsignificant reduction in incidence was observed for other organ-specific diseases, including invasive cervical cancer and Hodgkin disease (HD) [7]. Torres *et al.* [8] observed that, at a New York City hospital, the percentage of hospitalized HIV-1-infected patients who had OIs was unchanged in the HAART era.

We reviewed several large studies that evaluated the effectiveness of HAART in terms of the incidence of AIDS-defining illnesses. As shown in Table 2, these studies produced contrasting results; while some studies reported a reduction in the incidence of AIDS-defining illnesses, others reported no change or an increase in the incidence of AIDS-defining illnesses, particularly OIs [3,6,9,10].

In particular, Dore *et al.* [10], in a large recent study, observed that HAART had an impact on *Mycobacterium avium* complex (MAC) infection and cytomegalovirus (CMV) disease, whereas they noted a significant increase in PCP and tuberculosis. Lederberger *et al.* [11] evaluated

Table 3 The common organ-specific manifestations in the HAART era

Organ	Organ-specific manifestations
Lung	Bacterial pneumonia
Brain	HIV-1 encephalitis
Heart	Pericarditis
Kidney	Focal glomerulosclerosis (HIVAN)
Gut	Enterocolitis
Liver	Chronic HCV hepatitis
Oral cavity and skin	Oral candidiasis and bacterial folliculitis
Eye	Retinal microvasculopathy
Cutaneous and mucosal system, and lymph nodes	Non-Hodgkin lymphoma and Hodgkin disease

HCV, hepatitis C virus.

AIDS-related OIs after starting HAART in 2410 HIV-1-infected patients. They showed that the risk of developing an OI is greatest during the initial months of therapy. Moreover, the incidence of certain OIs, including oesophageal candidiasis, nontuberculosis mycobacterial infection, CMV disease and non-Hodgkin lymphoma, decreased significantly, but only after 3 months of HAART, whereas the incidence of other OIs, including PCP, toxoplasmosis and Kaposi's sarcoma (KS), decreased within 3 months of starting HAART. Thus, it should be noted that some OIs still occur despite virologically successful HAART, while other OIs still occur mainly in patients who have not had access to therapy or who failed antiretroviral therapy.

Similarly, accumulating evidence suggests that successful suppression of HIV RNA does not translate into decreased replication of hepatitis C virus (HCV) [12], and inflammation and fibrosis from HIV and HCV coinfection worsened during antiretroviral therapy [13]. It should be noted that most retrospective and prospective studies concerning the impact of HAART on the incidence of AIDS-defining illnesses did not fully clarify the frequency of AIDS diagnoses and the frequency of mortality related to these illnesses.

However, the introduction of HAART has seen the emergence of several complications, termed immune reconstitution inflammatory syndrome (IRIS), including CMV vitritis, MAC lymphadenitis, paradoxical responses to treatment for tuberculosis, and exacerbation of cryptococcosis [6]. This syndrome seems to be an unmasking of an undiagnosed OI, or an exacerbation of a diagnosed OI in the setting of improved immune function that contributes to the pathogenesis of the OI.

Although OIs produce particular organ-specific manifestations during the course of the disease, other organ-specific manifestations may be sustained by the HIV-1 itself, such as HIV-associated nephropathy (HIVAN), cardiomiopathy, HIV-1 encephalopathy and wasting syndrome. The widening of the clinical spectrum of organ-specific manifestations during the HAART era is also influenced by other factors, including undiagnosed HIV-1 infection and an increasing proportion of patients diagnosed late with HIV-1.

With the introduction of HAART and its widespread use over the last few years, several concerns regarding organ-specific manifestations have been raised which are still to be addressed. One issue which has to some extent been resolved is the interruption of primary and secondary prophylaxes against opportunistic pathogens, including PCP, MAC, *Cryptococcus neoformans* and *Toxoplasma gondii* in patients successfully treated with HAART. Some concerns are yet to be addressed regarding interruption of maintenance therapy, including disseminated MAC infection, cerebral toxoplasmosis and extrapulmonary cryptococcosis in patients under treatment with HAART.

In this review, we analyse the influence of HAART on several organ-specific manifestations, particularly OIs, cerebral disorders and HIV-1-related malignancies, as not all HIV-1 organ-specific manifestations are decreasing in the HAART era.

Organ-specific manifestations before and after the introduction of HAART

Pulmonary manifestations

In the last few years, it has become apparent that the lung is an important niche for the replication of HIV-1, which may have implications for HAART. The lung is a major site for opportunistic pathogens, such as PCP, *Mycobacterium tuberculosis* and pyogenic bacteria. Wolff *et al.* [14] have clearly shown that PCP has been a less common diagnosis since HAART became available, whereas bacterial pneumonia has been more common in patients treated with HAART than in those treated in the pre-HAART era. In contrast, another study found a significant decrease in bacterial pneumonia in patients treated with HAART [15]. No difference was found in the incidence of CMV pneumonia in HIV-1-infected patients receiving or not receiving HAART [14]. In addition, Jones *et al.* [16] observed that the risk for tuberculosis was much lower among patients treated with HAART, and they pointed out that widespread use of HAART does reduce the risk of tuberculosis, and may help bring about further declines in tuberculosis among HIV-1-infected patients. Finally, the impact of HAART on pulmonary malignancies has not been fully investigated. Wolff *et al.* [14] showed a significant increase in non-Hodgkin lymphoma in patients receiving HAART compared with the pre-HAART era. Similarly, the incidence of HIV-1-related lung cancer increased from

0.8/100 patient-years in the pre-HAART era to 6.7/100 patient-years in the post-HAART era [17].

Neurological and psychiatric disorders

HIV-1 infection is often complicated by neurological disorders in the advanced stage of the disease. Some investigators have reported a decrease in the incidence and prevalence of OIs of the central nervous system (CNS), which may be correlated with the use of HAART since 1996 [18,19], whereas during the pre-HAART era neurological disorders were the initial manifestations of AIDS in 7–20% of patients [20]. In a recent study, Neuenburg *et al.* [21] confirmed a decreased incidence of OIs of the CNS, including toxoplasmosis, CMV infection and cryptococcosis. In particular, a progressive reduction in the incidence of cerebral toxoplasmosis was observed in the HAART era [21–23], but this infection still tended to occur regularly in patients with advanced immunosuppression, especially in those patients who failed HAART.

The impact of HAART has also been investigated with regard to other neurological disorders, such as HIV-1 encephalopathy, primary CNS lymphoma, progressive multifocal leukoencephalopathy (PML) and distal symmetric polyneuropathy. An autopsy study showed increased HIV-1 encephalopathy from 1982 to 1993, and persistence of mild HIV-1 encephalopathy from 1994–1998 [24]. Thus, in the HAART era there has been a persistent increase in mild and moderate HIV-1 encephalopathy, whereas severe HIV-1 encephalopathy, which was uncommon in the pre-HAART era, has not been observed at all in the HAART era [21]. The trend towards an amelioration of HIV-1 encephalopathy in the HAART era might be explained by direct inhibition of HIV within the brain, as well as improvement of immunological markers, by HAART; moreover, HAART may lead to suppression of inflammatory neurotoxins within the brain [25].

HAART prolongs life by restoring immune responses to non-HIV-1 pathogens, but does not prevent direct HIV-1-related pathology in the brain, so long-term survival appears to increase the risk of HIV-1 encephalopathy.

Maschke *et al.* [23] have observed a significant reduction in the prevalence of HIV-1-associated distal symmetric polyneuropathy during the HAART era. These investigators suggested that HAART may be effective in this pathology through the suppression of macrophage activation and neurotoxin production in the peripheral nerve [26]. Another interesting aspect of neurological disorders in the HAART era is the decline of primary CNS lymphoma [21,27]. In addition, immune recovery induced by HAART in patients with primary CNS lymphoma leads to improvement in the survival of these patients [28].

Whereas the incidences of most neurological disorders have reduced since HAART was introduced, the incidence of PML has not significantly changed between the pre-HAART and HAART eras [21,29,30]. In addition, PML outcome has been found to be poor in both HAART-naïve and HAART-experienced patients who responded to anti-HIV treatment [29]. It should be noted that PML has been associated with immune reconstitution [6], and that immune reconstitution as a result of HAART does not, paradoxically, worsen the course of PML [30].

Finally, psychiatric disorders, including acute psychosis, mainly develop in patients with advanced HIV-1 infection, with a wide incidence range of 0.2–15% [31]. This wide range of incidence of psychiatric disorders is probably a result of varying clinical selection criteria for the patient population, the fact that these studies were mainly conducted in psychiatric wards, and finally varying diagnostic criteria for mental illnesses.

In a retrospective study, we evaluated the impact of HAART on acute psychosis [32]. Our study showed a significant increase of acute psychosis during the HAART period. Since HAART has prolonged life expectancy, it can be postulated that the risk of mental disorders may reflect the proportion of HIV-infected individuals suffering from various chronic mental conditions.

Cardiac involvement

Cardiac involvement is commonly reported in HIV-1-infected patients, especially in those in the advanced stage of the disease [33]. Before the HAART era, pericarditis was the most frequent clinical cardiac involvement observed in the AIDS population [34], caused by specific organisms such as *M. tuberculosis*, *Streptococcus pneumoniae* or *Staphylococcus aureus* [35]. In addition, cardiac involvement with cardiomyopathy, myocarditis and endocarditis was often related to opportunistic pathogens [36]. The course of HIV-1 infection, and particularly cardiac involvement, has been profoundly modified by the introduction of HAART, with OIs being less frequent and survival having been prolonged.

Pugliese *et al.* [37], in a retrospective study, showed cardiac involvement in 282 of 544 patients (51.8%) before the HAART era, but in only 93 of 498 patients (18.6%) during the HAART era. A significant reduction of pericarditis, dilated cardiomyopathy, and ischemia was observed in patients treated with HAART, although pulmonary hypertension significantly increased during the HAART era. However, pericarditis remains the commonest cardiac involvement in the HAART era [37].

In the last 7 years, the increased and long-term use of protease inhibitors (PIs) has raised concerns about an

increased risk of coronary heart disease [38]. Retrospective studies in large numbers of patients have produced conflicting results [39–42]. More recently, in a large, prospective observational study of about 23 500 HIV-1-infected patients, Friiss-Moller *et al.* [43] observed a 27% increase of risk factors for myocardial infarction for each year of HAART exposure up to 7 years. They also pointed out that overall myocardial infarction remains relatively rare (126 events in 23 500 patients).

HIV-associated nephropathy

In the last 10 years, renal diseases have become frequent complications of HIV-1 infection, and the number of patients starting dyalisis has increased by 20% per year [44]. In addition, HIV-1-related renal diseases were found to be the forth leading cause of end-stage renal disease among black men aged 20–64 years [45].

HIV-associated nephropathy (HIVAN) is the most common HIV-1-related renal disease [46], and it is probably related to a direct effect of HIV-1 on the kidney. Other renal lesions are membranous glomerulonephritis, immunoglobulin A (IgA) nephropathy, and haemolytic uremic syndrome [46–48]. No effective treatment has been found, and the majority of patients with HIVAN become dyalisis-dependent.

Several case reports and case series show the beneficial effect of antiretroviral therapy on slowing the progression of renal diseases. Monotherapy with zidovudine resulted in better renal outcomes in patients with HIVAN [49]. Recent case reports support the effectiveness of HAART, particularly PIs [50,51], in renal function in one patient with HIVAN, and in two patients with membranous nephropathy, respectively. More recently, Szczech *et al.* [52] reviewed the clinical courses of 19 HIV-1-infected patients with HIVAN or other HIV-related renal diseases. They showed beneficial effects of PIs in association with prednisone on the progression of these nephropathies. From these studies, it is difficult to determine whether this benefit is related to the specific use of antiretroviral drugs in suppressing viral replication, inasmuch as HIVAN involves a direct effect of HIV-1 expression in cells of the kidney [53].

In the pre-HAART era, the prognosis for HIV-1-infected patients with end-stage renal disease was poor, with the mortality rate reaching 50% 1 year after starting dyalisis [54]. In the HAART era, the mortality rate is still more than 30% 1 year after starting dyalisis [45]. Despite the potential beneficial effects of HAART, Schwartz *et al.* [55] estimate that the exponential increase in the number of patients with improved quality of life and life expectancy will result in a similar expansion in the number of HIV-1-infected patients who progress to end-stage renal disease.

However, it should be noted that some antiretroviral drugs, including a PI, indinavir, and a nucleoside reverse transcriptase inhibitor (NRTI), tenofovir, may cause nephropathy. In particular, renal intolerance of indinavir is a rare but important complication in HIV-1-infected patients, and several cases of acute renal failure, renal atrophy and interstitial nephritis have been reported [56]. Karras *et al.* [57] have recently reported three cases of renal toxicity associated with the use of tenofovir, including renal failure, proximal tubular dysfunction, and nephrogenic diabetes insipidus.

Gastrointestinal manifestations

Gastrointestinal disease has been one of the most common features of HIV-1 infection, and since HIV-1 particularly affects the mucosal immune system, the gastrointestinal tract is a target for several OIs as well as various HIV-1-associated diseases.

OIs are the most frequent gastrointestinal manifestations of AIDS, including oesophageal disease, enterocolitis, and biliary tract and pancreatic diseases, and remain a major cause of morbidity and mortality in HIV-infected patients [58,59]. Before the introduction of HAART, the most common oesophageal disease was oesophagitis caused by *Candida albicans*, CMV and herpes simplex virus (HSV). Diarrhoea is frequently observed during the clinical course of the disease [60]; the most common pathogens isolated were protozoa such as *Criptosporidium* and *Microsporidium*, viruses such as CMV, adenovirus and coronavirus [61], and bacteria, including *Clostridium difficile*, *Shigella flexeneri*, *Salmonella* spp., and *Campylobacter* spp. [60,62].

Monkemuller *et al.* [60] have evaluated the effect of HAART on the prevalence of gastrointestinal OIs in HIV-1-infected patients evaluated endoscopically over a 3-year period. They observed a marked reduction of gastrointestinal OIs, including CMV infection, oesophageal candidiasis, bacterial colitis and *C. difficile* colitis, in HIV-1-infected patients, and more interestingly the clearance of OIs in these patients after HAART therapy was achieved despite persistently low CD4 cell counts. Several authors have also shown that HAART can restore immunity to *Cryptosporidium parvum* and *Enterocytozoon bieneusi* in HIV-1-infected patients, resulting in complete clinical, microbiological and histological resolution [63,64].

With increasing use of HAART, gastrointestinal OIs are becoming uncommon findings for patients with AIDS. However, it should be remembered that OIs may still occur in AIDS, especially when patients access care late in the course of the disease, or are not adherent with therapy, or

when resistance of HIV to antiretroviral drugs develops. It is well known that most antiretroviral drugs are often associated with gastrointestinal side-effects, including nausea, vomiting and diarrhoea, and these effects are the most frequently cited reason for discontinuation of HAART [65].

Thus, in the era of HAART, diarrhoea still occurs as a manifestation in HIV-1 patients; despite the relatively small percentage of hospitalizations due to diarrhoea, this clinical manifestation can have a debilitating impact on HIV-1-infected patients [66].

Liver manifestations

Hepatobiliary manifestations of HIV-1 infection are common but rarely fatal. The liver is a reservoir for HIV-1 infection and a target organ for several OIs.

Before the introduction of HAART, mycobacterial infection of the liver was the most common infection diagnosed on liver biopsy in HIV-1-infected patients. MAC and *M. tuberculosis* were more frequently isolated in patients with a CD4 cell counts lower than 50 cells/μL [67]. In addition, the liver is involved in other opportunistic infections caused by CMV, *T. gondii*, *Leishmania* spp., and *C. neoformans*.

After the introduction of HAART, as discussed above, a dramatic reduction was observed in disseminated infections, mainly caused by *Mycobacterium* spp., CMV and *C. neoformans*, and consequently a reduction in liver OIs was also observed.

However, a critical issue remains concerning coinfection of HIV with various hepatotropic viruses in the era of HAART. Several studies have shown that HIV-1 affects outcome for patients with chronic HBV and HCV infections [68,69].

In fact, HIV-1 infection, along with an impaired cell-mediated response, produces increased HBV replication, increased HBV DNA and consequently a reduced response to interferon-alpha therapy. The impact of HAART on chronic viral hepatic infections has been extensively investigated for HCV infection, and to a lesser extent for HBV infection. Restoration of immunity to chronic HBV infection may occur after HAART, yet HAART may increase the rate of progression of liver disease in HIV-1-infected patients, through an increase in cytotoxic T cells, PI liver toxicity or transaminase levels [70]. Moreover, HAART has been suggested to provoke HBV reactivation, either as a result of direct effects of HAART or the accumulation of immune escape mutants [71].

HAART has improved survival rates among HIV-1-infected patients, but increased mortality related to progression of chronic HCV infection and liver failure has been reported [69,72]. There are conflicting data on the effect of HAART on the course of HCV viraemia and liver disease in HIV-1-infected patients. Some studies have shown no significant changes in HCV RNA and alanine aminotransferase serum levels during HAART [73,74]. We have confirmed these results, and we also observed that, in a group of patients who showed increased levels of alanine aminotransferase during HAART, HCV RNA levels did not further increase [75]. In contrast, other investigators reported transient or persistent increases in HCV load during HAART [76,77]. In particular, Babik *et al.* [78] demonstrated that, after long-term HAART, patients had a higher HCV load and increased quasispecies diversity, suggesting that HAART drives HCV to evolve more rapidly in an attempt to create escape mutants.

Other investigators showed that HAART induces a decline or clearance of HCV RNA serum levels, and this is an encouraging finding for coinfected patients because responsiveness to interferon-alpha therapy seems to be inversely correlated with serum HCV RNA levels [79,80].

Finally, we may speculate that effects of HAART associated with different characteristics of the immune response and HCV disease may explain the conflicting results that have been reported to date.

Mucocutaneous manifestations

Oral and cutaneous manifestations are present in virtually all patients with HIV-1 infection at some point in the course of their disease. The clinical spectrum of HIV-1-related oral and cutaneous manifestations has changed over the last 15 years through increasing use of prophylactic drugs to prevent AIDS-related OIs, and, most importantly, through availability of HAART.

The most frequent oral manifestation observed in HIV-1-infected patients before the introduction of HAART was oral candidiasis, while other common oral manifestations included oral hairy leukoplakia, herpese simplex labialis, gengivitis-periodontitis, and KS [81,82].

KS has an high incidence in HIV-1-infected patients, and it is the most common cancer occurring in these patients [83]. In the last 5 years, several studies have evaluated the impact of HAART on the incidence of cancers in HIV-1-infected patients. They showed a dramatic decline in the incidence of KS in patients treated with HAART, and this decline may continue as new, more effective antiretroviral agents are developed and widely used [84–86].

However, it is still unclear whether the treatment effect results from the direct action of antiretroviral agents on HIV-1, which is known to trigger KS, or represents a direct antiviral potency against human herpesvirus 8. Sgadari *et al.* [87] showed that administration of the PI indinavir or

saquinavir to nude mice blocked the development and induced regression of angio-proliferative KS-like lesions promoted by primary human KS cells.

Oral manifestations of HIV-1 are changing in the era of HAART; in particular, oral candidiasis, herpes simplex labialis, oral KS and periodontal disease decreased by more than 30% after the introduction of HAART [82,88]. However, HSV infection, salivary-gland disease and oral warts, along with oral candidiasis, appear to persist with HAART therapy [89,90].

The spectrum of dermatological findings related to HIV-1 also includes a variety of cutaneous disorders. The most frequent diagnoses before the era of HAART were seborrheic dermatitis, dermatophytosis of the skin, folliculitis, papular pruritic dermatitis, herpes simplex and zoster virus infections, and scabies [91,92]. *S. aureus* is the most common bacterial skin pathogen affecting HIV-1-infected patients [91]. After the introduction of HAART, there was also a change in the morbidity of cutaneous disorders in HIV-1-infected patients.

Calista *et al.* [93] showed a significant decrease in cutaneous disorders in patients treated with HAART; in particular, there was a reduction in the incidence of cutaneous infections from 301 of 456 patients (66%) not treated with HAART to 266 of 502 patients (53%) treated with HAART, whereas the incidence of adverse cutaneous drug reactions rose from 8% to 20% in those patients treated with HAART. However, it should be noted that staphylococcal infections of the skin remain a frequent and common cutaneous disorder in the era of HAART [91].

Ocular manifestations

Ophthalmic manifestations of AIDS fall into two major categories: vascular disease of the retina and other tissues and OI of the retina and choroid.

The most common vascular lesions in HIV-1-infected patients are 'cotton-wool' spots, characteristic manifestations of a diffuse retinal microvasculopathy and retinal ischemia [94].

Infections of the retina and choroid vary in prevalence, but CMV retinitis was the most common intraocular infection in HIV-1-infected patients before the introduction of HAART. In an autopsy study, Morinelli *et al.* [95] showed that CMV retinitis was by far the most common retinal infection in these patients, with all other infections probably accounting for $\leq$5% of retinal infections. The second most common infection of the retina was necrotizing retinitis, caused by varicella-zoster, and the third most common was retinochoroiditis, caused by *T. gondii*. In a large retrospective study, Jalali *et al.* [96] observed a dramatic decrease in the incidence of CMV retinitis after the introduction of HAART, representing a 99% reduction since 1993. In addition, much longer remission duration from recurrent CMV retinitis has been reported after the introduction of HAART, and the minimal HIV-1 viral load reached after the initiation of HAART therapy appears to be more important in one retrospective study, because all the studies addressing discontinuation of maintenance therapy were based mainly on CD4 cell count [97]. Thus, the introduction of HAART has had a major impact on the natural history of CMV retinitis, with improved survival time and decreased risk of progression following diagnosis. However, complications of CMV retinitis such as retinal detachment, uveitis and optic atrophy have also frequently occurred in the era of HAART [98].

Lymphoproliferative manifestations

HIV-1-infected patients are at increased risk of developing malignancies of lymphoid origin. Non-Hodgkin lymphoma (NHL) and HD may occur with increased incidence, as recently reported in a large study including 47 936 HIV-1-infected patients [84].

A statistically significant reduction in the incidence of NHL has been demonstrated since the widespread introduction of HAART, although this reduction has not been as dramatic as that for KS [84,99]. Because most patients respond to HAART with significant increases in CD4 cell counts, at the population level the overall incidence of NHL is expected to decrease [100]. However, it is unclear whether HAART is fully effective at reversing the B-cell stimulation that is associated with HIV-1 infection, and represents a risk factor for NHL. Ratner *et al.* [101] showed that concomitant use of standard chemotherapy and HAART in HIV-1-infected patients with NHL was effective and safe. In addition, the incidence of all subtypes of NHL has decreased significantly, especially for primary brain lymphoma and immunoblastic lymphoma, in the era of HAART [84].

In a large study, Glaser *et al.* [102] evaluated 1752 HIV-1-infected patients, and found HD in 13% of the patients diagnosed in the pre-HAART era and in 12% of the patients diagnosed in the post-HAART era. These results confirmed the findings of a previous large prospective study that demonstrated no statistically significant change in the incidence rates for HD in patients treated or not treated with HAART [84].

Genitourinary manifestations

Advanced HIV-1 infection is associated with an increase in cervical squamous intraepithelial lesions and infection with oncogenic human papillomavirus (HPV) genotypes.

Heard *et al*. [103] demonstrated that HAART may result in a significant reduction of cervical squamous intraepithelial lesions despite the absence of clearance of HPV infection.

No study has yet addressed the ultimate effect of HAART on prevention of invasive cervical cancer. Lillo *et al*. [104] showed that the risk of HPV infection and the risk of squamous intraepithelial lesions both increased with declining CD4 cell count, and there were no differences in terms of persistence of high-risk HPV infection of squamous intraepithelial lesions. A large prospective study demonstrated that there was no substantial change in the incidence of cervical cancer in HIV-1-infected patients treated with HAART [84].

Bacterial infection of the urinary tract is very common in patients with HIV-1 infection. De Gaetano Donati *et al*. [105] evaluated the effect of HAART on the incidence of bacterial urinary tract infection in HIV-1-infected patients during two periods: before HAART (1992–1995) and after HAART (1997–2000). They showed a significant reduction in the incidence of bacterial urinary tract infection in these patients, when HAART became the standard therapy.

Future directions

The era of HAART has produced some novel and unexpected developments. Firstly, long-term survival of HIV-1-infected patients treated with HAART has probably led to an increased incidence of mild and moderate HIV-1 encephalopathy (Table 3). In a more recent study, Chang *et al*. [106] suggested that the persistent brain abnormalities in patients with HIV-1 encephalopathy after 3 months of HAART may be a result of reactive inflammatory processes in the brain, and that regimens with two cerebrospinal fluid-penetrating antiretrovirals drugs do not appear to be more effective than those with one cerebrospinal fluid-penetrating drug. Further investigations are needed to better understand the inflammatory processes and molecules involved.

HIVAN remains the most common HIV-1-related renal disease in the era of HAART, notwithstanding that antiretroviral drugs have shown beneficial effects on this renal disease (Table 3). However, additional studies are required to evaluate the risk factors for HIV-1-related renal diseases, in particular population-based studies, studies employing increased use of renal biopsy, and large-scale clinical, prospective and controlled trials to test older and newer antiretroviral drugs.

In the future, HIV/HCV coinfection will be a major issue for HIV-1-infected patients treated or not treated with HAART (Table 3). With the introduction of therapy with pegylated interferon-alpha and ribavirin, the combined treatment approach to HIV/HCV must be investigated in depth to address several concerns, including the timing of the two combined treatments (HAART and pegylated interferon-alpha plus ribavirin), the hepatotoxic effects of HAART in patients with chronic HCV infection, and the pharmacological interactions between antiretroviral agents and anti-HCV drugs.

There is a need to further investigate the effects of HAART on certain malignancies, such as invasive cervical cancer and other non-AIDS-defining cancers, including HD, and squamous-cell carcinoma of the head, neck and anus. Mbulaiteye *et al*. [100] clearly showed that risk of cervical cancer was unrelated to CD4 cell count, and that elevated risks of non-AIDS cancers may be a result of lifestyle factors. Thus, these findings suggest that, in the future, new typical organ-specific manifestations may occur with increased frequency and may contribute to the epidemiology of OIs.

Effects of HAART on organ-specific manifestations: the immune reconstitution inflammatory syndrome (IRIS)

The IRIS represents a restored capability of the host to mount an inflammatory response against persistent microbial antigens, and leads to the development of symptoms in HIV-1-infected patients with new organ-specific manifestations [6,106]. The enhancement in the immune response to widely prevalent microorganisms, such as CMV and *Mycobacterium* spp., appears to be especially marked.

Table 4 summarizes the organ-specific manifestations with microorganisms and clinical disorders involved in the IRIS. The vigorous HAART-induced immune response can produce organ-specific lesions in unusual locations, and histological examination of these lesions shows an intense inflammatory response surrounding few, if any, microorganisms [6]. MAC was among the first organisms associated with this syndrome. The presence of granulomas suggests that the clinical manifestation is attributable to a restored inflammatory response. In addition, necrotic subcutaneous nodules, endobronchial tumours, small bowel involvement, and paravertebral abscesses have all been reported as MAC-related unusual lesions [6]. A retrospective review of patients with *M. tuberculosis* infection treated with HAART found an 8.7% prevalence of paradoxical CNS lesions, including intracranial tuberculoma [107]. There have been cases of mediastinal lymphadenitis, as well as subcutaneous abscesses associated with cryptococcal infection, that occurred months after the institution of HAART (Table 4). A new type of ocular disease in the setting of CMV infection was recognized after the introduction of HAART, which has been termed ‘immune recovery vitreitis’. The inflammatory

Table 4 Organ-specific manifestations and their aetiological agents in the immune reconstitution inflammatory syndrome

Organ	Microorganism	Disease
Lung	*Mycobacterium avium-intracellulare*, *Pneumocystis carinii*, *Cryptococcus neoformans*	Endobronchial tumours, mediastinal lymphadenopathy, necrotizing pneumonia, granulomatous pneumonia
Brain	*Mycobacterium tuberculosis*, *Mycobacterium avium*-intracellulare, JC virus	Tuberculoma, vertebral bone and paraspinal masses, inflammatory progressive multifocal leukoencephalopathy
Gut	*Mycobacterium avium-intracellulare*, *Mycobacterium tuberculosis*, herpes simplex virus	Colitis, cecitis, periproctitis
Skin	*Mycobacterium avium-intracellulare*, *Cryptococcus neoformans*, human herpes virus 8	Cutaneous nodules, subcutaneous abscesses, disseminated Kaposi's sarcoma
Eye	Cytomegalovirus, herpes zoster virus	Vitritis, retinal detachment, cataracts, iritis, cheratitis

response can induce proliferative vitreoretinopathy and posterior subcapsular cataracts [108]. Shelburne *et al.* [6] described a patient who had worsening of cutaneous KS coincident with immune recovery due to HAART.

An inflammatory progressive multifocal leuko encephalopathy (PMNL) variant has been reported to have developed in several patients treated with HAART; all the patients who developed PMNL in the setting of immune reconstitution have shown either improvement or at least stability of their neurological deficits [6].

Conclusions

This review summarizes current understanding of organ-specific manifestations in HIV-1-infected patients in the HAART era.

With the introduction of HAART there has been a striking reduction in the incidence of organ-specific manifestations caused by OIs, such as PCP, cerebral toxoplasmosis, CMV disease, oesophageal candidiasis, and pulmonary and extrapulmonary tuberculosis, and to a lesser extent those manifestations caused by HIV-1 itself, including HIVAN, HIV-1 encephalopathy, and HIV-1-related malignancies.

We believe it is likely that the widespread use of HAART, particularly the use of newer antiretroviral agents, will produce unique new effects on HIV-1-infected organ systems. Indeed, with increasing recognition of patients with immune reconstitution inflammatory syndrome, characteristic clinical presentations and new organ-specific manifestations have been reported; also, many patients who need HAART are not taking it, and many HIV-1-infected patients are unaware of their infection, and remain at high risk for organ-specific manifestations, including OIs.

In our opinion, one of the many challenges in the era of HAART will be to maintain vigilance for OIs, and to monitor new organ-specific manifestations to provide the best possible clinical outcome for HIV-1-infected patients.

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