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Clinical Manifestations of HIV Infection in the HAART Era

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Abstract

A notable change in the spectrum of clinical manifestations in HIV-infected subjects has been recognized over the past few years. The expanded use of HAART and the increased longevity of the HIV-infected population are the main factors accounting for this change. While the incidence of classical OI occurring in severely immunosuppressed patients has declined dramatically, conditions linked to the use or removal of antiretroviral agents are often seen nowadays. Likewise, complications derived from concomitant diseases such as chronic viral hepatitis and tumors are now more relevant due to the longer life expectancy of HIV-infected individuals.

Key words

HIV. Antiretroviral therapy. Toxicity. Inflammatory reactions. Clinical manifestations. Hepatitis.

Introduction

Twenty years after the recognition of AIDS, physicians caring for HIV-infected individuals are facing a notable change in the spectrum of clinical manifestations in their patients. With the advent of antiretrovirals, especially the implementation of highly active antiretroviral therapy (HAART), the clinical course of the disease has changed dramatically[1]. Typical AIDS conditions such as *Pneumocystis carinii* pneumonia or *Cytomegalovirus* (CMV) retinitis are now rarely seen in subjects under regular clinical follow-up. In fact, the main groups currently at risk for development opportunistic infections (OI) with their classical manifestations are patients who do not get a benefit from treatment, such as subjects non-adherent to therapy, or those reluctant to take drugs due to potential adverse events and/or high pill burden (Table I). Subjects with severe immune deficiency having been exposed to almost all antiretroviral drugs in the past, and failing their current regimen, might be added to this list. However, evidence exists supporting the protection against OI given by a not completely successful treatment[2].

In developed countries, newly diagnosed HIV+ patients developing a classical OI are often immigrants from undeveloped regions with a higher prevalence of HIV infection, or older individuals infected by a heterosexual route through casual contacts in the past (personal or that of the sexual partner)[3]. Lack of information and difficult access to HIV testing in the first group, and a wrong perception of the need to rule out HIV infection among the latter, explain this observation.

Although hospital admissions due to classical OI are declining, new complications are arising and account for a growing request for care by HIV-infected persons. On the one hand, the use of HAART has made patients to live long enough to eventually develop liver-related complications and certain tumors. A second subset of emerging complications has to do with the broad use of antiretrovirals. Short-term and long-term toxicities of these drugs, as well as unexpected symptoms after their introduction or removal, are now of greater concern. Table II sum-

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Table I. *Main groups at risk for developing classical HIV-related opportunistic infections*

Persons knowing their HIV infection
• Reluctant to take treatment
• Treatment failure with low CD4 counts
Persons unaware of their HIV infection
• Immigrants
• Other minority groups
• Individuals with past casual heterosexual contacts

marizes the conditions contributing to this new face of HIV disease.

Liver complications

Advanced liver disease

An overall prevalence of hepatitis C virus (HCV) co-infection of more than 30% exists among HIV-seropositive subjects[3,4]. Progression to end-stage liver disease, including cirrhosis[6,7] and hepatocellular carcinoma[8], occurs more rapidly in HIV+ subjects co-infected with HCV. With the increase in the life span of HIV-infected subjects, liver complications are becoming one of the leading reasons for hospital admissions and death among co-infected patients[9-13].

Therefore, two major consequences can be inferred. First, a close follow-up of chronic hepatitis C along with that of HIV infection is needed, and treatment of chronic hepatitis C should be considered a priority in co-infected subjects[14]. On the other hand, HIV care providers need to be aware of the higher risk of hepatotoxicity of antiretroviral drugs in subjects with chronic viral hepatitis[15,16].

Hepatitis B exacerbations

Lamivudine (3TC) is widely used for the treatment of both HIV and HBV infections. In contrast to what is seen for HIV, 3TC-resistant HBV strains emerge slowly, and are seen in about 25% of subjects after one year of therapy[17]. Flares in transaminase levels due to HIV relapses have been described in chronic HBV-infected subjects after developing genotypic 3TC resistance[18]. Similar hepatitis flares have been noticed after removal of 3TC from the antiretroviral regimen[18].

Tumors

HAART-induced immune reconstitution is adequate to prevent malignancies associated with profound immune suppression, but does not affect those disorders which characteristically occur at higher CD4 cell counts[19]. Moreover, the longevity associated with HAART may extend the window of vulnerability to a variety of malignancies. While there has been a striking reduction in the incidence of Kaposi's sarcoma (KS) and some types of lymphomas over the past few years[20,21], several studies have shown that the incidences of AIDS-related lymphomas and cervical cancer have not changed appreciably[22-25].

AIDS-related lymphoma

Lymphoproliferative disorders seen in HIV-infected individuals comprise a heterogeneous group of conditions, some of which are linked to specific herpes viruses, such as Epstein-Barr virus (EBV) and human herpes virus 8 (HHV-8), and occur at varying levels of immune suppression[24-26]. Therefore, they have been affected differently by the introduction of HAART. Thus, while the incidence of systemic, diffuse large-cell and primary CNS lymphomas appears to be reduced in the HAART era, no clear reduction is evident for Hodgkin's disease and Burkitt's lymphoma[23,27]. Therefore, the risk of AIDS-related lymphoma in the HAART era has been reduced in the stratum of patients with CD4 cell counts <50 cells/μl, but has been unchanged in higher CD4 strata[23].

Anogenital cancer

The outcome of human papillomavirus (HPV)-associated anogenital lesions has not changed significantly since the introduction of HAART. The role of immunosuppression is probably low in the development-maintenance of these virus-related lesions, which share similar risk factors and routes of transmission with HIV. On the contrary, the increased longevity of HIV-infected subjects may count more in the susceptibility to develop malignant lesions.

Antiretroviral drug-related toxicities

Current guidelines recommend the use of at least three antiretroviral drugs for the treatment of HIV infection. Given the sustained benefits of HAART, an increasing number of HIV-infected patients are receiving multiple drugs for prolonged periods of time. In addition, the licensing process of many antiretroviral agents has been accelerated, often with little being known about their long-term safety. As a consequence, a fair number of drug-related toxicities are being increasingly recognized.

While a comprehensive review of antiretroviral toxicity is beyond the scope of this article and can be found elsewhere[34], some aspects deserve particular attention due to their novelty or clinical impact.

Mitochondrial toxicity

This is a family-specific toxicity linked to nucleoside and nucleotide-analogue reverse-transcrip-

Table II. *New clinical spectrum of HIV infection in the HAART era*

A) Emerging conditions
1. Liver complications in HCV ± HBV-infected patients
   - End-stage liver disease
   - Hepatocellular cancer
   - Hepatitis B exacerbations following development of resistance to or withdrawal of 3TC
2. Tumors
   - Lymphomas (herpes virus)
   - Anogenital cancer (human papillomavirus)
   - Non-virus-related tumors

B) Treatment-related complications
1. Toxicities
   - Drug-specific
   - Hypersensitivity rash (ABC, NVP, EFZ, DLV, APV)
   - Mitochondrial toxicities (NRTIs and NtRTIs)
     - Peripheral neuropathy (D4T, ddC, ddI, 3TC)
     - Pancreatitis (ddI, ddC, 3TC)
     - Lactic acidosis (AZT, D4T, ddI, ddC)
     - Cardiomyopathy and myopathy (AZT)
   - Emerging
     - Hepatotoxicity
     - Lipodystrophy
     - Hyperlipidemia and insulin resistance
     - Avascular necrosis and osteopenia
2. Inflammatory reactions
   - Infectious
     - *Mycobacterium avium* complex
     - *Mycobacteryum tuberculosis*
     - *Cytomegalovirus*
     - HCV and HBV
     - Herpes Zoster and simplex
     - Progressive multifocal leukoencephalopathy (JC virus)
     - Other
   - Tumoral
     - Kaposi's sarcoma
     - Lymphoma
   - Autoimmune
     - Graves disease
     - Systemic lupus erythematous
     - Autoimmune thyroiditis
   - Miscellany
     - Sarcoidosis
     - Castleman disease
3. Retroviral rebound syndrome

3TC: lamivudine; ABC: abacavir; NVP: nevirapine; EFZ: efavirenz; DLV: delavirdine; APV: amprenavir; NRTIs: nucleoside-analogue reverse transcriptase inhibitors; NtRTIs: monophosphorylated nucleotide-analogue reverse transcriptase inhibitors; D4T: stavudine; ddC: zalcitabine; ddI: didanosine; AZT: zidovudine; IDV: indinavir.

tase inhibitors (NRTI and NtRTI, respectively), and it is due to the inhibition of mitochondrial enzymes that generate ATP[33,34]. Major mitochondrial toxicities include myopathy, neuropathy, hepatic steatosis and lactic acidaemia, pancreatitis, and possibly also peripheral lipoatrophy.

Lactic acidosis is one of the most serious mitochondrial toxicities, with a mortality of 80% among patients with plasma lactate levels above 10 mmol/l. It has an incidence of 1.3/1000 persons-year and appears within months after initiating treatment. Symptoms include malaise, nausea, vomiting, abdominal pain and hyperventilation. It evolves to liver failure and refractory rhythm disorders. There is an increase in lactic acid, anion gap and liver enzymes and a decrease in bicarbonate, along with macrovesicular steatosis. Besides the standard treatment of lactic acidosis, riboflavin has been shown to decrease lactic acid concentrations over a few days.

Although lactic acidosis is rare, lactic acidaemia is far more common and is often associated with mild constitutional symptoms, mild increases in transaminases, and peripheral lipoatrophy.

Hepatotoxicity

The use of HAART may be limited by the development of severe hepatic cytolysis[24]. The incidence of severe cytolysis in the context of HAART varies among cohorts, as do their risk factors[15,16,36-38]. Data from the major studies published suggest that antiretroviral-related liver enzyme elevation occurs more often in HIV-1+ patients co-infected with HBV and/or HCV virus. The contribution of individual antiretroviral agents is less clear. While some authors have observed a higher incidence of liver toxicity when protease inhibitors (PI) are given, compared to dual nucleoside therapy[36,37], others have found an association only with some of them, in particular ritonavir (RTV)[16]. Regarding NNRTI-based regimens, nevirapine (NVP) has been linked to a higher incidence of transaminase elevation; cases of severe abnormalities in liver enzymes have been reported with

efavirenz (EFZ) as well[39-41]. At least two mechanisms seem to be involved in the NVP-associated hepatic injury. The first occurs a few days to several weeks after initiating NVP in the context of a hypersensitivity reaction and often involves other organs. The second type of hepatic injury is recognized several months after being on NVP[16,42]. It is limited to the liver and might represent an intrinsic toxic effect of NVP.

Lipodystrophy syndrome

The occurrence of abnormalities in fat distribution and in the metabolism of lipids and sugar in HIV+ individuals receiving HAART was reported for the first time in 1998[34]. What is known as "lipodystrophy syndrome" comprises a number of features that may appear when using different antiretroviral combinations. The main body shape abnormalities are peripheral fat loss (lipoatrophy in the face, limbs and buttocks) and central fat accumulation (within the abdomen, breasts, and over the dorsocervical spine [so-called "buffalo hump"], as well as other lipomata). Metabolic features include hypertriglyceridemia, hypercholesterolemia, insulin resistance (raised C-peptide and insulin concentrations) and type 2 diabetes mellitus. Dyslipemia at concentrations associated with increased risk for cardiovascular disease occurs in about 70% of patients. While both protease inhibitors and NNRTI are associated with hyperlipidemia, lipoatrophy seems to be linked to the mitochodrial toxicity of NRTI. Nevertheless, the exact contribution of each antiretroviral to the development of body shape abnormalities has not been well elucidated, and there may be various other factors that concur in the pathogenesis of such body changes.

This syndrome has become a major issue in the management of the HIV-infected patients. Adherence to antiretroviral therapy often is compromised because of the cosmetic effects, leading to virological failure. On the other hand, the metabolic effects may lead to an increase in cardiovascular disease. While other classical risk factors may be present, the use of HAART might contribute to premature coronary-artery disease in patients with few or no risk factors when receiving HAART[43,44]. Although several hypotheses have been proposed, the pathogenesis of the syndrome remains unknown. The lack of a case definition and the unknown role of the different drugs/classes and of demographic factors, impact negatively on the management of the syndrome. For the time being, diet, use of lipid-lowering agents and exercise are some of the recommendations proposed. The benefit of switching to PI-sparing regimens remains to be established, although preliminary studies have shown a partial amelioration of symptoms after the switch[45,46]. Lipid levels, particularly of triglycerides, tend to decrease when PI are replaced, but the morphologic abnormalities do not significantly improve[47].

Avascular necrosis and osteopenia

An increased incidence of avascular necrosis (AVN) in HIV-infected subjects on HAART has been noticed over the past few years[48]. Its occurrence is probably underestimated[49]. Although PI have been involved in the pathogenesis of AVN, cases have been described in HIV-infected individuals never exposed to PI[48-53]. The question has arisen of whether it is HIV infection itself, HIV therapy, or some other factors (such as history of steroid treatment and hyperlipidemia) that produce the increased risk for the development of AVN among HIV patients. In a recent report, this risk was estimated to be 58 times the rate expected in the general population[53].

Unexpectedly higher rates of bone demineralization in patients receiving HAART have been noticed recently[54-55]. Subjects on PI-based therapy might suffer osteopenia more often compared to those under other drugs or without treatment (40-50 *vs.* 20-23%). However, available data are too preliminary to conclude that bone mineral loss is related to PI intake.

Inflammatory reactions after initiation of HAART

The immune restoration which follows the introduction of HAART may actually promote the clinical expression and/or development of OI, as well as AIDS-related malignant conditions and other non-infectious diseases. Although the recognition of some of these conditions might merely represent the progression of previously quiescent disorders, which coincidentally became symptomatic after initiation of HAART, there is strong supporting evidence that HAART precipitated them in most instances. An acute inflammatory reaction as a result of rapid immune recovery most likely mediates this effect[56,57]. The clinical presentation of OI following the introduction of HAART adopts special characteristics, distinct from the classical forms (Table III). Of note, the symptoms improved over time even without discontinuation of HAART, although some patients required anti-inflammatory agents and specific antimicrobial therapy.

Mycobacterium avium complex

Patients developing *M. avium* complex lymphadenitys within 12 weeks of starting HAART have higher CD4 counts and are more likely to develop a localized draining sinus, and are less likely to have weight loss and disseminated disease[58]. Other uncommon presentations of *M. avium* complex such as granulomatous masses, osteomyelitis, bursitis, Addison disease and skin nodules have been reported[59,60]. Treatment with antimycobacterial agents, corticosteroids and/or local surgical drainage, provides a favorable outcome while patients continue with their antiretroviral therapy.

Mycobacterium tuberculosis

The development of inflammatory reactions several weeks after beginning anti-tuberculosis treatment is well known, but clearly seems to be fostered

Table III. *Differences in clinical presentation of some opportunistic infections in HIV-infected patients with and without highly active antiretroviral therapy*[57]

Opportunistic Infection	Common clinical presentation	Presentation after HAART
Mycobacterium avium complex	Disseminated disease, weight loss, diarrhea, mycobacteremia	Focal lymphadenitis, granulomatous masses; mycobacterial rare
Cytomegalovirus	Retinitis, vitritis uncommon	Vitritis, retinitis, extraocular disease
Cryptococcus neoformans	Meningitis occasionally indolent, CSF leukocytosis uncommon	Overt meningitis, marked CSF leukocytosis
Progressive multifocal leukoencephalopathy	Neurologic deficits, MRI hypodensities without contrast enhancement	Neurologic deficits; MRI hypodensities, frequently with peripheral enhancement
Herpes zoster	May be severe, accompanied by complications	Mild presentation, uncomplicated

CSF: cerebrospinal fluid; MRI: magnetic resonance imaging

by concomitant HAART[61,62]. Paradoxical reactions may include new fever, worsening or emergence of lymphadenopathy, pulmonary infiltrates, or pleural effusion[63]. All these complications improve or resolve, either spontaneously or after adding anti-inflammatory agents to HAART.

Cytomegalovirus

Cytomegalovirus (CMV) retinitis, as well as extraocular CMV infections, have been reported after initiation of HAART[64,65]. Typically, an inflammatory reaction accounts for a large part of the new symptoms, as demonstrated by the occurrence of vitritis in patients treated with HAART who previously had CMV retinitis[66]. Most cases improved, regardless of therapy.

Hepatitis B and C viruses

Liver damage in subjects with chronic hepatitis B and/or C is basically immune mediated. The immune deficiency caused by HIV results in a lessened inflammatory reaction in the liver of co-infected subjects, although fibrosis seems to be accelerated both for HBV[67] and HCV[6,7]. This blunted immune response against HBV and HCV antigens is rapidly restored as a consequence of the immune reconstitution associated with HAART. Not surprisingly, this enhanced inflammatory response to HBV or HCV may cause episodes of acute hepatitis in people known to be chronic carriers[68-71].

Herpes viruses

The incidence of herpes zoster is increased shortly after initiating HAART[72]. In one series, nearly 8% of HIV+ patients who began HAART developed first or recurring herpes zoster. The clinical manifestations of zoster tend to be mild and complications are unusual. Subjects experiencing a more pronounced increase in CD8+ cells after HAART is initiated seem to be particularly prone to develop herpes zoster.

Progressive multifocal leukoencephalopathy

The diagnosis of progressive multifocal leukoencephalopathy (PML), a demyelinating cerebral disease caused by the JC virus, has rarely been made soon after initiation of HAART[73]. Individuals with very low CD4 counts at baseline are at higher risk. Although also very unusual, worsening of symptoms in subjects with a prior diagnosis of PML may occur following HAART[74]. In any case, clinical symptoms tend to wane while antiretroviral therapy continues and immune recovery takes place.

Other infections

Enlargement of lymph nodes in subjects with a past history of disseminated histoplasmosis after initiation of HAART has been reported[75]. Likewise, first or recurring cryptococcal meningitis developing in temporal association with initiation of HAART has been described[76].

Patients with pre-existing warts, or *molluscum contagiosum,* may experience intense, local inflammatory reactions after HAART initiation, evolving to spontaneous resolution of the skin lesions after a few weeks in most cases. Pathology exam shows vigorous local inflammatory responses with mononuclear cell infiltrates[75].

Non-infectious disorders

Some non-infectious conditions may be exacerbated by the immune reconstitution caused by HAART[57]. Patients with lymphoma or Kaposi's sarcoma may experience a sudden enlargement of their lesions following initiation of HAART. Likewise, exacerbations of autoimmune disorders such as Graves disease, autoimmune thyroiditis, and systemic lupus erythematous have also been observed in HIV-positive persons who began HAART. More rarely, other processes of unknown etiology such as Castleman disease and sarcoidosis, have also been described soon after beginning HAART[57,77].

Retroviral rebound syndrome

Typical symptoms of acute HIV infection such as fever, malaise, pharyngitis, skin rash, myalgias, and tender adenopathies, may appear within 2-6 weeks after stopping antiretroviral therapy in subjects who had previously achieved complete virological HIV suppres-

sion under HAART[78,79]. A rapid increase in plasma HIV-RNA is uniformly seen in all these patients, resembling what occurs in primary HIV infection, when no immunological control has yet developed. Symptoms are most likely a direct consequence of the high level of virus replication and the development of cellular immune responses to the virus, leading to massive cell lysis and cytokine release. As occurs in true acute HIV infection, the decline in HIV viremia and resolution of symptoms parallel the emergence of HIV-specific cytotoxic T lymphocytes[80,81]. Hypothetically, subjects having long-term, complete virological suppression under HAART might have lost their specific anti-HIV immune responses. In this context, those able to mount a rapid and potent cytotoxic T-lymphocyte response when facing HIV again will develop symptoms. Therefore, the retroviral rebound syndrome may be more common in patients with relatively high CD4 counts experiencing an abrupt rebound of HIV replication after cessation of antiretroviral drugs. This phenomenon may become more widely observed as more patients are tempted by the possibility of "drug holidays" and as trials of structured interruption of therapy are being conducted.

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