Redefining AIDS: Towards a Modification of the Current AIDS Case Definition

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AIDS is defined by the occurrence of an opportunistic infection or tumor considered indicative of advanced infection with human immunodeficiency virus (HIV). Even though recent modifications have improved the widely used AIDS case definition issued by the World Health Organization and the Centers for Disease Control and Prevention, the modified version has fallen short of generating a globally functional instrument for the surveillance of HIV-related infections. The clinical AIDS case definition should be as comprehensive as possible. In many countries, only the diagnosis of an AIDS-defining illness will grant the affected patient social benefits or access to medical care. An expanded AIDS case definition is also likely to improve surveillance of HIV-associated morbidity and mortality; increase the awareness of emerging infections; increase the number of clinical endpoints in clinical trials; and facilitate the introduction of diagnostic tests, screening programs, and preventive measures. Examples of opportunistic infections and tumors that could be considered in future modifications of the AIDS case definition are discussed in detail.

Infection with HIV is characterized by progressive immunodeficiency. As the CD4 cell count declines, affected patients become susceptible to a variety of opportunistic infections (OIs). HIV-associated OIs are usually defined as infections that cause increasingly frequent and/or increasingly severe disease among HIV-infected persons as a result of immunosuppression [1]. The diagnosis of AIDS is based on the presence of selected OIs that occur during advanced HIV infection.

During the beginning of the AIDS epidemic in the United States, HIV predominantly affected Caucasian men who have sex with men. Early AIDS case definitions reflected this circumstance because they listed diseases that were typically encountered in this population [2–4]. However, in terms of a global context, homosexual Caucasian American men now represent only a fraction of the population affected by HIV.

In recent years, even in the United States, the epidemiology of HIV infection has changed; women and intravenous drug users are increasingly being affected by the disease. The 1993 modification of the Centers for Disease Control and Prevention (CDC) classification reflected the changing epidemiology of HIV infection by introducing three new AIDS-defining events into the AIDS case definition. These events, which are more common in nonhomosexual patients, include cervical carcinoma, recurrent bacterial pneumonia, and pulmonary tuberculosis [5]. Even though the introduction of these three new entities has improved the AIDS case definition, the classification has fallen short of generating a globally functional instrument for the surveillance of HIV-related infections. The World Health Organization (WHO)/CDC classification is used in many countries even though certain HIV-associated diseases that are not listed may be more common in these areas than are the illnesses listed in the current classification.

In some countries (including the United States and Germany), the diagnosis of an AIDS-defining infection entitles a patient to social benefits or grants access to medical care. In many countries, limited resources prevent the use of immunological endpoints (i.e., a CD4 cell count of <200 cells/µL) as indicators of AIDS. Other nations, including Canada and all countries of the European community, have for other reasons (such as more inclusive health insurance systems compared to those in the United States) renounced the use of laboratory criteria as indicators of AIDS. In countries that do not use immunologic criteria, the clinical AIDS case definition needs to be as comprehensive as possible to be functional.

Because the 1993 classification was not issued exclusively by the CDC but (for the first time) also by the WHO, the urgency of including diseases that may be less common in the United States but represent important causes of HIV-associated morbidity and mortality in other areas of the world becomes even more obvious. Several examples of opportunistic infections and tumors that could be considered for future modifications of the classification are discussed in the following paragraphs and are listed in table 1.

HIV-Associated Diseases Currently Not Classified as AIDS-Indicating Illnesses

Parasitic Infections

Microsporidiosis. Microsporidiosis has emerged as an important infection in severely immunocompromised patients
with AIDS [6, 7]. Two genera of microsporidia, Encephalitozoon and Enterocytozoon, are responsible for most human infections. The most frequently detected microsporidian is Enterocytozoon bieneusi, which is isolated from the gastrointestinal tract of as many as 40% of AIDS patients with chronic diarrhea [8-18]. As a result of protracted enteric illness, E. bieneusi infection can result in life-threatening dehydration and electrolyte imbalances as well as malabsorption and serious weight loss.

To date, three Encephalitozoon species have been reported to infect patients with HIV infection: E. hellem, E. cuniculi, and E. (formerly Septata) intestinalis [6, 7, 19-32]. All of these species have been documented to cause disseminated disease involving the eyes [21, 25, 27], upper and lower respiratory tracts [23, 24, 27], upper and lower gastrointestinal tracts [26-28], and gastrointestinal and hepatobiliary [19, 20, 29-31] tracts of affected patients. These infections are often severe and occasionally result in respiratory or renal failure [23, 28, 32]. Fatal outcomes have been reported in some cases [7, 24].

Microsporidia have been detected in HIV-infected patients from Australia, Europe, Africa, Asia, South America, and North America. Standard staining methods are readily available or can easily be established in any institution [7]. The experience from some centers, including mine, where microsporidia now represent the most prevalent enteropathogen isolated from patients with HIV-associated diarrhea, suggests that classification of microsporidiosis as an AIDS-defining illness will significantly increase the number of reportable AIDS cases in many areas of the world.

Only two cases of E. bieneusi infection have been reported in immunocompetent patients; both were self-limited. Increased awareness of this infection is likely to result in a future increase in the number of reports of non-HIV-infected patients with microsporidiosis. However, chronic or extraintestinal manifestations are not expected to occur in this patient population.

It has become obvious that microsporidia are an important cause of HIV-associated morbidity and mortality. Chronic microsporidiosis (i.e., an episode that lasts ≥4 weeks) or disseminated microsporidiosis is highly indicative of advanced immunodeficiency and, therefore, like cryptosporidiosis, should be classified as an AIDS-defining illness.

Cyclospora cayetanensis infection. Cyclospora cayetanensis is another protozoan capable of causing diarrhea in healthy and immunocompromised patients [33-39]. The diarrhea is watery, associated with crampy abdominal pain, and, at least in immunodeficient patients, often characterized by cyclic remissions and exacerbations [33]. Cyclosporiasis, like cryptosporidiosis, is self-limited in immunocompetent patients [33, 35], but HIV-infected patients are likely to develop a protracted and more-severe illness [37-39]. Relapses are commonly observed in immunocompromised patients who do not receive secondary prophylaxis [37]. Established staining techniques are available in most institutions, as staining for cryptosporidia will also detect cyclospora.

Cyclosporiasis is rare in Europe and the United States, but a substantial number of reportable cases must be expected from areas such as Haiti and South America that have been severely affected by the AIDS pandemic. For example, in a Haitian study of 450 HIV-infected patients with diarrhea, Cyclospora was isolated from 11% of the diarrheal specimens [37], making this protozoan one of the most prevalent HIV-associated enteropathogens in this area. Chronic cyclosporiasis (i.e., an episode that lasts ≥6 weeks) or relapsing cyclosporiasis should be considered AIDS-defining events.

Visceral leishmaniasis. This infection affects ~400,000 persons annually [40]. In areas where leishmaniasis is endemic, a prevalence as high as 1-10 cases per 1,000 population has been recorded [41-43]. Epidemiological studies with use of serological tests in Brazil indicated that 7.5% of children are infected with Leishmania species each year [41]. Similar figures have been reported for Kenya [43].

While the clinical presentation of visceral leishmaniasis in immunocompetent hosts is quite characteristic and the onset of the disease usually occurs within weeks to months after a trip to countries where the infection is endemic, HIV-associated leishmaniasis often causes great diagnostic difficulties. Typical symptoms such as fever, hepatosplenomegaly, weight loss, and lymphadenopathy as well as pancytopenia and hypergammaglobulinemia are common in patients with AIDS. These symptoms therefore are often not attributed to leishmaniasis because they can usually be caused by HIV itself or by a broad spectrum of other opportunistic pathogens, which may delay diagnosis in some cases despite a rather typical presentation.

Serological surveys indicate that only a minority of infected individuals develops clinically apparent visceral disease that is associated with the symptoms mentioned above. Prospective studies have shown that the ratio of patients with clinical disease to asymptptomatically infected patients, as evidenced by seroconversion or skin test reactivity, ranges from 1:6.5 to

<table>
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<th>Opportunistic infections:</th>
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<tr>
<td>• Chronic microsporidiosis (episodes lasting &gt;4 weeks) or disseminated microsporidiosis</td>
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<td>• Chronic Cyclospora cayetanensis infection</td>
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<td>• Disseminated Penicillium marneffei infection</td>
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<td>• Relapsing or extranodal bartonellosis</td>
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<td>• Cerebral or disseminated Trypanosoma cruzi infection</td>
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<td>• Rhodococcus equi infection</td>
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<td>• Relapsing or chronic visceral leishmaniasis</td>
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Opportunistic tumors:

• Anal carcinoma
• Leio sarcoma or leiomyosarcoma (Epstein-Barr virus positive) in children
• Relapsing or extranodal Hodgkin’s disease (Epstein-Barr virus positive)
mon opportunistic HIV-associated infection in some areas of HIV infection [56], making leishmaniasis the third most common infection as compared with non-HIV-infected patients. Almost 50% of the cases in Spanish adults are already associated with leishmaniasis. Patients coinfected with leishmania and HIV have a substantially increased risk of developing active leishmaniasis. Therefore fail to report such trips. Because reactivation of latent disease may occur many years after infection, patients often do not recall pertinent travels, or treating physicians fail to connect the current illness with remote trips to areas where leishmaniasis is endemic. Furthermore, patients often do not realize that mosquito bites received in countries such as Italy, France, Spain, or Portugal, where visceral leishmaniasis is hypoendemic, may cause diseases that cannot be contracted in Germany or the United States and therefore fail to report such trips.

The diagnosis of leishmaniasis in immunodeficient patients depends on direct visualization of the parasite in affected tissues. Stains are readily available for this purpose [46]. The development of parasite-specific cellular immunity and the ability to generate sufficient amounts of IFN-γ, IL-2, and IL-12 are critical for recovery from leishmaniasis in mice and humans [49–55]. Predominance of these so-called Th1-type cytokines leads to activation of macrophages and enhanced intracellular killing of parasites, whereas the predominant Th2-type cytokines, such as IL-4 and IL-10, is associated with progressive disease [50]. The secretion of beneficial Th1-type cytokines (IFN-γ, IL-2, and IL-12) is known to be severely impaired in patients with advanced HIV infection; specific cytotoxic and helper T cell responses characterized by the expansion of antigen-specific CD4+ and CD8+ T cells are diminished, and macrophage function is compromised. Both T cell depletion and cytokine dysregulation therefore render immunocompromised HIV-infected individuals highly susceptible to disseminated leishmanial disease.

Because leishmaniasis is hypoendemic in these areas, a number of cases will continue to occur in non-HIV-infected patients. However, chronic or relapsing leishmaniasis is rare in immunocompetent adults, whereas >50% of HIV-infected patients with leishmaniasis have a chronic relapsing course despite adequate therapy with antimonials [46, 57, 58]. This is especially true in patients with more-advanced immunodeficiency. In one report from Germany, 80% of the HIV-infected patients who survived the initial episode had one or more relapses [46]. This contrasts sharply with the expected 10% relapse rate reported among immunocompetent patients from the Mediterranean area [58]. In accordance with the literature [59–61], these observations underscore the importance of lifelong secondary prophylaxis for visceral leishmaniasis in patients with advanced immunodeficiency, as would be recommended for most HIV-associated infections.

The prognosis for HIV-infected patients with leishmaniasis is poor. Although most patients die of AIDS-related causes, leishmaniasis may contribute to the poor outcome either by causing immunosuppression independent of that due to HIV [62, 63–65] or by stimulating HIV replication via activation of infected CD4+ lymphocytes and macrophages [66].

Until now, leishmaniasis has not been considered an AIDS-defining complication of HIV infection, even though leishmaniasis obviously constitutes a common manifestation of HIV infection in southern European patients with AIDS. The additional case load to be expected is probably substantially higher than 500 cases (the approximate number reported in the literature, as these cases are only a fraction of the cases that must have occurred in the past years. For example, 90 episodes of HIV-associated leishmaniasis have been diagnosed at a single institution in Spain in just 8 years, while many other hospitals in the same area have never published reports of any cases [61]. Leishmaniasis is also endemic in parts of India, a country with a rapidly growing number of HIV-infected patients.

Visceral leishmaniasis that occurs in association with HIV infection should be reported to national surveillance institutions to facilitate the assessment of the magnitude of this problem. Relapsing or chronic visceral leishmaniasis should be categorized as WHO/CDC stage C.

**Chagas’ disease.** Infection with Trypanosoma cruzi is increasingly being recognized as an opportunistic infection [67–74]. Immunologic defense against *T. cruzi* is mediated mainly by T lymphocytes, and the presence of AIDS is therefore a factor likely to favor reactivation of *T. cruzi* infections. Patients with AIDS and Chagas’ disease often present with distinct clinical features that are uncommon in other patient populations. In a recent review of the pathology of concurrent HIV infection and *T. cruzi* infection, 87% of the patients were found at autopsy to have severe, multifocal or diffuse meningoencephalitis with necrosis and hemorrhage in association with a high parasite load in affected tissues [70].

In contrast, meningoencephalitis is uncommon in patients without AIDS who have fatal, vector-transmitted or trans-
sion-associated *T. cruzi* infections or who have been accidently exposed to the pathogen in the laboratory. Chagas’ disease is associated with pseudotumoral cerebral lesions only in immunocompromised patients; these lesions are often accompanied by perilesional edema in the cranial cavity that results in intracranial hypertension. The appearance of these lesions is virtually indistinguishable from that of cerebral neoplasms or infections often encountered in patients with AIDS, such as primary non-Hodgkin’s lymphomas of the brain or cerebral toxoplasmosis.

As with leishmaniasis, a substantial number of reactivated *T. cruzi* infections must be expected in the future in association with the continuous spread of the HIV epidemic in Latin America. However, exact data on the prevalence of this association are lacking. To obtain more information on the association between HIV infection and *T. cruzi* infection, all cases of cerebral, disseminated, or relapsing Chagas’ disease should be reported to national surveillance centers and should be classified as AIDS-defining events.

**Fungal Infections**

*Penicillium marneffei* infection. *Penicillium marneffei* is an obligate pathogenic dimorphic fungus that rarely infects immunocompetent persons [75–77]. After the first description of a human *P. marneffei* infection in 1973 [77], only 13 further cases were diagnosed before 1983 [75, 76]. The dramatic increase in the number of *P. marneffei* infections after 1983 coincided with the alarmingly rapid spread of the AIDS pandemic in Southeast Asia [78]. To date, >200 cases have been reported that have occurred almost exclusively in HIV-infected patients in Southeast Asia [78–87]. Meanwhile, *P. marneffei* has become the third most common opportunistic infection in AIDS patients in northern Thailand [79]. Other areas of endemcity in Southeast Asia include the Guangxi Province of China [75, 83, 88], Hong Kong [80, 87, 89], Indonesia, and Vietnam [75]. Additional cases have been reported in immunocompromised patients in the United States [90], Australia [91], and Europe [92–97]. All these patients had a history of travel to Southeast Asia.

The reported mortality associated with penicilliosis is high, exceeding 75% in most series [75, 76, 80, 81]. Early diagnosis of *P. marneffei* is therefore of utmost importance. Readily available, established histological staining and culture methods are used for diagnosis. The highest sensitivity for isolation of *P. marneffei* has been reported for bone marrow specimens (26 of 26 cases) and lymph node biopsy specimens (9 of 9 cases) [79]. Skin biopsy specimens (47 of 52 cases), blood cultures (59 of 78 cases), and sputum cultures (14 of 41 cases) were found to be less sensitive for establishing the diagnosis.

As with other OIs, complete eradication of *P. marneffei* probably can not be achieved in patients with AIDS [81]. Therefore, oral maintenance therapy with itraconazole (100–200 mg b.i.d.) is recommended to prevent recurrence of the infection after successful initial treatment. In view of the rapid spread of the AIDS pandemic in Southeast Asia, classifying disseminated *P. marneffei* infection as an AIDS-indicating disease would facilitate AIDS surveillance in this area, resulting in more reliable epidemiological information from this “hot spot” of the epidemic.

**Bacterial Infections**

*Bartonellosis. Bartonella quintana* and *Bartonella henselae* are increasingly recognized as agents of severe and occasionally fatal disease in HIV-infected patients [98–100]. *B. henselae* infection is usually associated with cat bites or scratches, and domestic cats have been documented as a major natural reservoir of this pathogen. The contemporary environmental source of *B. quintana*, the bacterium that gained widespread attention as the agent of trench fever during World War I, remains unknown. It has been known for some time that both species can cause bacillary angiomatosis (BA), a vascular proliferative disorder that has been documented exclusively in HIV-infected patients. BA was first described in 1983 and has been categorized as a “minor” OI (group B disease) in the 1993 revised CDC classification of HIV infection [5].

Since the initial report of BA, the spectrum of bartonellosis in HIV-infected patients has expanded continuously and now comprises entities such as relapsing bacteremia with fever; meningitis; endocarditis; and angiomatic lesions of the spleen, lung, brain, bone, and liver [98–100]. The latter entity is known as peliosis hepatitis. Molecular methods for the diagnosis of bartonellosis have been established in reference centers, but in most institutions diagnosis depends on visualization of the bacteria in affected tissues with use of a silver stain. Because silver stains are available but not routinely used in most laboratories, increased awareness is likely to result in a higher detection rate.

In immunocompetent patients, infection with *B. henselae* can result in cat-scratch disease, a granulomatous disease of skin and lymph nodes; however, in HIV-infected patients, *B. henselae* causes BA. The reason for the different host response (granuloma vs. angioproliferative) in immunocompetent patients and immunodeficient patients is unknown. Prolonged treatment (>3–4 months) is necessary for HIV-infected patients; lifelong secondary prophylaxis is recommended for patients who relapse after a >4-month course of treatment. Even though the expected additional case load is probably not high, bartonellosis causes distinctly different and more-severe manifestations in HIV-infected patients than in immunocompetent hosts, making it a specific marker of advanced immunodeficiency. Relapsing and extracutaneous bartonellosis should therefore be categorized as an AIDS-defining illness (group C disease).

*Rhodococcus equi* infection. This gram-positive, intracellular, weakly acid-fast coccobacillus was initially isolated from horses but is increasingly recognized as an important pathogen
in immunosuppressed human hosts [101–103]. Sixty of 65 cases described in a recent review occurred in immunosuppressed patients, most of whom were infected with HIV [101]. The lung is the most common primary site of infection, but disseminated infections have been documented in patients with AIDS. Intracellular gram-positive coccobacilli are easily demonstrated in affected tissue specimens.

*R. equi* grows well on routine nonselective media at 35°C, but many cases of infection due to this organism may have previously been missed or discarded as contamination because the organism resembles commensal oropharyngeal diphtheroids. Relapses of this infection after discontinuation of therapy are common, and lifelong secondary prophylaxis is often required.

Classification of *R. equi* infection as an AIDS-defining event would likely enhance awareness of these pathogens and reduce their misclassification as commensals. The expected case load will probably be low despite the fact that rhodococcal infection is certainly underdiagnosed. However, established infection is clearly a specific marker of immunosuppression.

**Tumors**

*Human papillomavirus–associated anal cancer.* The presence of AIDS increases the risk of developing human papillomavirus (HPV)–associated neoplasms [104, 105]. This is true for both men and women, but until now, only cervical cancer—but not anal cancer—was included in the AIDS case definition. The decision was justified on the basis of studies that showed an increased prevalence of cervical dysplasia, a precursor lesion of cervical cancer [5, 104]. Prevalence data for cervical or anal cancer were not even presented in the official report of the CDC [5]. The incidence of anal cancer among homosexual men with AIDS is ~1 case per 1,000 persons, compared with 12 cases per 100,000 HIV-negative homosexuals or 7 cases per 1,000,000 persons in the general male population [104].

Higher rates of treatment failure and recurrence of HPV-associated cervical intraepithelial neoplasia have been reported for HIV-infected women [106, 107] and must also be expected for men with penile or anal intraepithelial neoplasms. Whereas recurrence of the lesions in HIV-seronegative women is associated with increasing severity of the initial lesion, recurrence in HIV-seropositive women is predominantly associated with severe immunosuppression [107].

Homosexual men with advanced HIV infection are at least four times more likely than non-HIV-infected homosexual men to have detectable anal HPV [108]. The risk of anal cancer is 2.9 times greater for homosexual men with CD4 cell counts of <500/mm³ than for those with higher counts, indicating that HIV-induced immunosuppression may influence the progression of HPV infection to intraepithelial neoplasia [109]. In a recent prospective study of 158 HIV-seropositive homosexual men and 147 HIV-seronegative homosexual men, the investigators similarly concluded that HIV infection was a strong predictor of the development of high-grade squamous anal intraepithelial neoplasms [110]. Immunosuppression remained an independent predictor of the development of these neoplasms in HIV-infected patients, even after adjustment for type of HPV and viral load.

The association between HIV and HPV, however, is more complex and not fully explained by immunosuppression and common behavioral risk factors. For instance, it has been shown that the HIV *tat* upregulates HPV 16 transcription and early gene expression [111, 112]. It is therefore not surprising that a recent study found a strong association between HIV and HPV that was evident early on, even in persons with normal CD4 cell counts. However, a further increase in the incidence of HPV infection was noted among persons with CD4 cell counts of <300/mm³ [113].

The above evidence argues for the inclusion of anal cancer as an AIDS-defining event in the current classification. The decision to include cervical cancer but not anal cancer is difficult to sustain, considering recently published data.

*Epstein-Barr virus–associated soft-tissue tumors.* Several authors have reported the occurrence of leiomyosarcomas and leiomyomas in children and young adults with HIV infection [114–120]. The tendency toward sarcomatous involvement of the gastrointestinal tract and lungs that has been noted among these patients is striking, and it is unusual in non-HIV-infected patients. Epstein-Barr virus (EBV) DNA is detected in most tumors from HIV-infected patients but not in leiomyomas or leiomyosarcomas from non-HIV-infected patients [114].

Similar observations have been reported for children undergoing organ transplantation [121], which supports the hypothesis that EBV-associated soft-tissue leiomyomas and leiomyosarcomas truly are opportunistic tumors in children and young adults. The number of reportable cases will probably remain low. However, as the number of HIV-infected children continues to grow worldwide, any improvement in the AIDS case definition for children might be important, considering the difficulties in using immunologic endpoints for diagnosing AIDS in children.

*Hodgkin’s disease.* In the largest study of AIDS-associated malignancies, investigators found that solid tumors did not occur more often in HIV-infected persons than in the general population [122]. The results of this study have been used widely as an argument that neither HIV nor HIV-associated immunodeficiency initiates or promotes the growth of tumors other than Kaposi’s sarcoma or non-Hodgkin’s lymphoma. However, if one takes a closer look at this study, it becomes evident that the incidence of two types of neoplasms (i.e., anorectal carcinoma and Hodgkin’s disease) was significantly increased.

Similar observations have been reported from Europe, where investigators from France and Italy detected a high prevalence of Hodgkin’s disease, predominantly among their intravenous drug–using patients [123, 124]. Another study from the United States found an excess incidence of Hodgkin’s disease of 19.3
cases per 100,000 patient-years in a cohort of homosexual HIV-infected men in comparison with the incidence in the general population [125].

The best argument for a role of HIV in the development of Hodgkin’s disease, however, is not the increased incidence of Hodgkin’s disease but the different natural history of the disease and therapeutic response observed for HIV-infected patients. HIV-infected patients are more likely to present in advanced stages of Hodgkin’s disease [126], which argues against improved surveillance as the reason for the observed association. HIV-infected patients more often present with extranodal disease including involvement of the gastrointestinal tract and bone marrow. More of these patients complain of B symptoms, and they respond less favorably to cytoreductive therapy [126].

While nodular sclerosis is the predominant subtype of Hodgkin’s disease among young non-HIV-infected patients (>80%), >40–50% of HIV-infected patients have Hodgkin’s disease of the mixed-cellular type. Furthermore, it has been noted that EBV is detected more often in the Reed-Sternberg cells of HIV-infected patients with Hodgkin’s disease. In one study, EBV genome was detected in >90% of the samples from HIV-infected patients [127], whereas the frequency of EBV genome in samples from non-HIV-infected patients has been reported to range from 30% to 60%.

In summary, there seems to be sufficient evidence to justify classification of relapsing Hodgkin’s disease as an AIDS-indicating tumor.

**Rationale for a Modification of the Current AIDS Classification**

Some infectious agents such as *Mycobacterium tuberculosis*, *Salmonella* species, *Cryptosporidium parvum*, *Cryptococcus neoformans*, and *Histoplasma capsulatum* affect both immunocompetent and immunocompromised patients. The same is true for many of the diseases discussed in this report. Cytosporangi-asis, leishmaniasis, *P. marneffei* infection, bartonellosis, trypanosomiasis, anal carcinoma, and Hodgkin’s disease all potentially affect both HIV-infected and non-HIV-infected patients. However, not only are these diseases more prevalent in patients with AIDS, but more important, the clinical courses of these diseases in HIV-infected patients are clearly different from those observed in non-HIV-infected patients.

Atypically invasive forms of some of the diseases mentioned above are considered indicative of HIV-induced immunosuppression and are regarded as sufficient criteria for diagnosing AIDS in the absence of other predisposing conditions. Examples include recurrent nontyphoidal salmonella bacteremia, chronic cryptosporidiosis, and extrapulmonary histoplasmosis and cryptococcosis. Similar criteria that define atypically invasive manifestations that are not expected to occur in immunocompetent patients can easily be established for the diseases presented in this report (table 1).

**Table 2. Advantages and disadvantages of expanding the current AIDS case definition.**

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<th>Disadvantages</th>
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<td>Improved surveillance</td>
<td>Costs of implementing the revision</td>
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<td>Improved access to social benefits and medical care</td>
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<tr>
<td>Increases awareness of HIV-associated illnesses</td>
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<td>Introduction of diagnostic tests, screening programs and preventive measures</td>
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<td>More clinical endpoints in clinical studies</td>
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<td>Increased complexity</td>
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<td>Psychological trauma and stigmas associated with the diagnosis of AIDS</td>
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Most of the diseases discussed herein also share other characteristic features of the established AIDS-defining infections. These features are as follows: (1) latent disease reactivates when immunodeficiency worsens; (2) the etiologic agent is an intracellular pathogen; (3) the cellular immune system is critical for containment of the disease; (4) the disease in HIV-infected patients follows a chronic relapsing course; and (5) secondary prophylaxis is mandated for patients with advanced immunodeficiency.

The reasons proposing a modification of the current AIDS classification are manifold (table 2). In many countries, AIDS-defining illnesses are reported to national agencies. Therefore, a precise AIDS case definition constitutes an important prerequisite for adequate surveillance. The importance of surveillance should not be underestimated: AIDS-defining events not only represent reportable diagnoses that can be used to issue monthly or yearly statistical analyses, but surveillance enables national and international agencies and governments to quantify needs with respect to medical resources and to optimize targeting of these resources.

As stated before, in many countries, including the United States and Germany, the diagnosis of an AIDS-defining illness entitles affected patients to social benefits. In some countries the diagnosis of an AIDS-defining illness may be the only means of access to medical care. To deny these benefits to some patients just because they have severe OIs that are clearly HIV-associated but are not included in the current AIDS case definition seems unjustifiable.

The classification of a certain disease as an AIDS-defining event is likely to increase awareness among treating clinicians as well as among other physicians such as pathologists, microbiologists, and radiologists who are involved in the care of HIV-infected patients. The methods for diagnosing all diseases discussed herein are readily available in most institutions. The failure to diagnose AIDS is not due to the unavailability of appropriate diagnostic methods but to the fact that treating physicians and involved microbiologists and pathologists do not order or use them.

For instance, at many institutions, the diagnosis of intestinal microsporidiosis is not pursued adequately despite the fact that
Specific diagnostic tests have been established that can be performed in any microbiology laboratory [7]. In any institution where microsporidia cannot be detected, as many as 40% of the etiologic agents of HIV-associated chronic diarrhea will be missed, with obvious consequences for the affected patient. Inclusion of microsporidiosis in the list of AIDS-defining illnesses would likely increase awareness of this prevalent disease and might also facilitate the introduction of appropriate diagnostic tests in more institutions. In some cases such a categorization might result in reimbursement for the diagnostic tests or the treatment of the disorder.

Inclusion of a certain disease in the AIDS case definition might also facilitate the introduction of screening programs, potentially resulting in the establishment of recommendations for preventive measures. Such an action will at least enable us to evaluate whether the institution of such programs would be beneficial.

A good example of this dilemma regarding screening can be found in the recent guidelines for the prevention of OIs in persons infected with HIV that were edited by the U.S. Public Health Service and the Infectious Diseases Society of America [128]. In the paragraph dealing with HPV-associated anal intraepithelial neoplasia and anal cancer in HIV-infected homosexual men, it is stated: “Although the risks for anal intraepithelial neoplasia (AIN) and anal cancer are increased among HIV-infected men who have sex with men, the role of anal cytological screening and treatment of AIN in preventing anal cancer in these men is not well defined.” The authors conclude that “therefore, no recommendations can be made for periodic and cytological screening for the detection and treatment of AIN.”

Even though this statement is honest and scientifically correct, it must have been distressing for the investigators to admit that adequate data are lacking, particularly since they were not discussing a rare disorder but a highly prevalent disease. The incidence of anal cancer among homosexual men with AIDS is ~1 case per 1,000 persons [104]. This incidence is more than 10 times higher than that of cervical cancer (for which there is an established screening program) among non-HIV-infected women (i.e., 8 cases per 100,000 persons).

Knowledge of the etiologic agent and the availability of established kits for its detection certainly make screening for anal dysplasia and carcinoma a feasible form of intervention. It is likely that such screening will also lower the incidence of HPV-associated morbidity and mortality and therefore prove cost effective, but we clearly need scientific data. The inclusion of anal carcinoma in the current AIDS case definition would facilitate the generation of the required evidence.

AIDS-defining events are often used as clinical endpoints in clinical studies. A more complete case definition will facilitate patients’ access to open-label treatment, which is usually granted when an AIDS-defining illness (the most commonly used endpoint) is diagnosed. A more complete definition would also shorten the time needed to generate a sufficient number of clinical endpoints, increase patients’ compliance, and speed up important research projects. These factors will become increasingly important because antiretroviral treatment options are broadening rapidly, and therapy is initiated earlier in the course of HIV disease. It will therefore become increasingly difficult to recruit a sufficient number of patients for trials with clinical endpoints in the United States, Europe, and Australia, countries where most previous studies were traditionally conducted.

An increasingly popular approach is to conduct smaller studies with surrogate markers as endpoints in countries with sophisticated laboratory facilities and to initiate so-called large simple trials at the same time. In these trials, large numbers of patients are evaluated only for the occurrence of clinical manifestations without assessment of immunological and virological data.

These trials often include patients from many countries who were previously exempt from participation in clinical studies. An example is SV 14604, an ongoing clinical trial for evaluating the benefit of a triple drug combination that includes saquinavir. Almost 6,000 patients were recruited in a large simple trial design. Some of the patients were recruited from countries in Africa, Southeast Asia, and Latin America. Although the concept of a worldwide trial was compelling, as this was the first chance for some patients living in countries with limited resources to gain access to antiretroviral therapies, the study has proved difficult to conduct.

The number of endpoints (defined as the occurrence of an AIDS-indicating infection) was smaller than anticipated, partly because many HIV-associated infections that occurred outside the United States did not meet the current AIDS case definition. This was a problem not only for countries in Latin America and Asia but also for my institution, where three of the first six HIV-associated infections observed in patients receiving the study medication (two patients with microsporidiosis and one with P. marneffei infection) were not considered AIDS-defining events and therefore did not qualify as endpoints. It is expected that broadening the AIDS case definition would ameliorate these problems.

One cannot deny, however, that an expansion of the current classification would also create problems. A more complete AIDS case definition will be more complicated and therefore more difficult to use in daily practice. Why should some pathogens, but not others, be included? A recent review of the literature listed 111 pathogens reported as more frequent or virulent in persons with HIV-related immunosuppression [1]. However, some of these descriptions were anecdotal, and the evidence for HIV-associated alteration of manifestations was often weak. It is therefore unlikely that the number of diseases proposed for inclusion in the AIDS case definition will render the case definition an incomprehensible and unusable list of illnesses.

Some patients experience the diagnosis of AIDS as psychologically traumatic or, at least, as a stigmatizing event. If physicians and psychologists are aware of this problem and are prepared to deal with it, the advantages of a broadening of
the AIDS case definition should outweigh the disadvantages, including the additional costs generated by the efforts necessary to change the definition.

**Conclusion**

HIV-associated OIs are defined as infections that cause increasingly frequent and/or severe disease due to immunosuppression in HIV-infected persons [1]. OIs most predictive of advanced HIV infection define AIDS [1]. In accordance with these definitions, the evidence I have presented is sufficient to change the definition. However, the selection of the diseases listed in table 1 was based on personal preference and expertise and is therefore admittedly biased and probably incomplete. The inclusion of some of the diseases listed may not be acceptable to other investigators. At any rate, I hope that the list as well as the concept behind it will stimulate further discussion that may pave the way towards a modification of the current classification. Such modification will result in a better, globally applicable instrument for the surveillance of AIDS.

**References**

4. Centers for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 1987; 36:35–14S.


