Acute Human Immunodeficiency Virus Type 1 Disease as a Mononucleosis-Like Illness: Is the Diagnosis Too Restrictive?

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The purpose of this study was to describe the frequency and duration of clinical features at the time of acute human immunodeficiency virus type 1 (HIV-1) disease in 218 patients with documented symptomatic primary HIV-1 infection. The mean duration of acute HIV-1 disease was 25.1 days (median, 20.0 days) and did not differ by gender, age, and risk factor. The frequency and mean duration of clinical features occurring in >50% of patients were as follows: fever, 77.1% and 16.9 days; lethargy, 65.6% and 23.7 days; cutaneous rash, 56.4% and 15 days; myalgia, 54.6% and 17.7 days; and headache, 50.9% and 25.8 days. Only 15.6% of patients presented with a typical mononucleosis-like illness (MLI) defined as fever, pharyngitis or sore throat, and cervical adenopathy, and 10% had no features of an MLI. A meningitis-like syndrome occurred in 20 patients (9.2%). Acute HIV-1 disease is more diverse than previously reported, and the absence of fever or other MLI features does not rule out acute HIV-1 disease.

Since the first reports of acute HIV type 1 (HIV-1) disease manifesting as an infectious mononucleosis-like illness (MLI) [1, 2], physicians have been alert to this diagnosis for populations at risk. Nevertheless, many cases may go unnoticed because this illness is not considered in the differential diagnosis, especially when signs and symptoms are atypical. Therefore, medical practitioners need to be aware of this illness in ambulatory practice [3–6].

The timing of identification of acute HIV-1 disease is crucial because early treatment reduces the incidence of complications [7, 8], and individual counseling to prevent further transmission must be initiated as patients with acute HIV-1 infection may be particularly contagious [9]. Published studies on acute HIV-1 disease contain only short descriptions of clinical features based on small sample sizes [10–16]. The objective of our investigation was to describe the frequency and duration of clinical features reported during acute HIV-1 infection in a large cohort of patients.

Patients and Methods

Patients

The patient population consisted of 218 symptomatic subjects enrolled in four prospective studies of HIV-1 seroconversion between 1985 and 1994. One hundred twenty-four patients were included in two cohorts coordinated by the National Centre in HIV Epidemiology and Clinical Research in Sydney (Australia): one cohort was from a prospective study of AIDS [17] that focused on homosexual men at risk of HIV seroconversion (67 patients), while the other was from a study that enrolled persons of both genders who were in all risk categories at the time of acute HIV-1 disease (57 patients). Fourteen Australian patients came from a European-Australian controlled trial on the treatment of primary HIV-1 infection [7]. In addition, 80 European patients were included: 52 from the Geneva part of the Swiss HIV Cohort Study [18] and another 28 from the European-Australian controlled trial [7] mentioned above. Each prospective study was approved by the respective ethics committee.

Biological and Clinical Assessment

The biological inclusion criteria were as follows: (1) the presence of p24 antigen in blood with negative or indeterminate serology (135 patients [62%]); (2) two bands on a western blot, one of which corresponded to the *env* gene (glycoprotein (gp) 160, gp 120, or gp 41), with negative or indeterminate serology

(18 [8%]); or (3) a negative HIV-1 screening test followed by a positive HIV-1 test within 1 year (median, 140.0 days) (65 [30%]). The symptoms and signs analyzed were reported by the patients themselves and/or by their treating physicians at the time of documented acute HIV-1 disease (criterion 1 or 2) or within the previous months (median, 65.0 days) before the first positive HIV-1 screening test (criterion 3). The clinical data were extracted from a review of standardized forms for data collection. We double-checked the data by examination of 190 available medical files (private and/or hospital).

We compared the duration of acute HIV-1 disease according to infection with zidovudine-sensitive (wild-type) HIV-1 or zidovudine-resistant (mutant) HIV-1. The most frequent genotype related to zidovudine resistance is a strain with a mutation at codon 215 of the reverse transcriptase gene [19]. It was detected by the method proposed by Larder et al. [19]. RNA was extracted and amplified by selective PCR analysis and then was reverse transcribed to complementary DNA with primer RT01 (5'-GTAGAATTCTGTTGAGTCAGATTGG-3'). The genotype determination was done on the first sample available after the onset of acute HIV-1 disease (median, 25.0 days) in 99 patients.

Statistical Analysis

Categorical variables are described in terms of frequency, and continuous variables are described as mean, median, and extreme values. The duration of acute HIV-1 disease was com-

Table 1. Characteristics of 218 patients with documented acute HIV-1 disease.

Characteristic	Value
No. (%) of patients with categorical variable	
Study population	
Australian	138 (63.3)
European	80 (36.7)
Gender	
Male	204 (93.6)
Female	14 (6.4)
Mode of infection (presumed)	
Homosexual contact	169 (77.5)
Intravenous drug use	9 (4.1)
Heterosexual contact	25 (11.5)
Other or unknown	15 (6.9)
Year of onset of acute HIV-1 disease	
≤1987	62 (28.4)
1988 to 1991	54 (24.8)
1992 to 30 June 1994	102 (46.8)
Mean (±SD) for continuous variable	
Age (y)	31.3 (7.8)
Median (range)	30.6 (18.5–64.8)
Duration* (d)	25.1 (22.2)
Median (range)	20.0 (3.0–184.0)

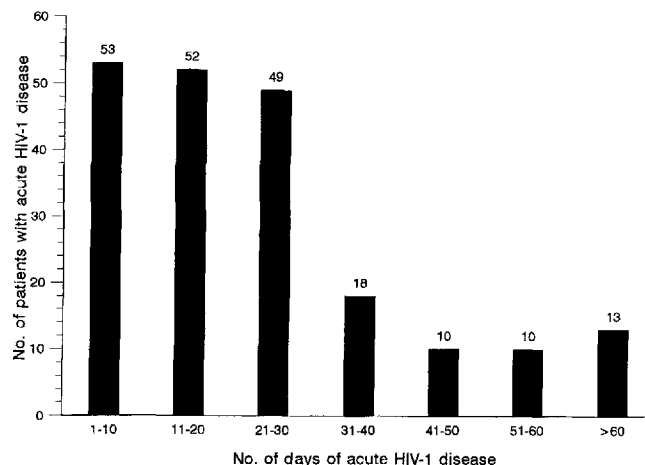* The duration of acute HIV-1 disease was available for 205 patients.

Figure 1. Distribution of the duration of acute HIV-1 disease in 218 patients.

pared by the Mann-Whitney U test, Student's t-test, and one-way analysis of variance after logarithmic transformation. A two-tailed P value of <.05 was considered significant. The statistical analysis was performed with SPSS version 6.0 (SPSS, Chicago) for Windows (Microsoft, Redmond, WA).

Results

The characteristics of the patients are listed in table 1, and the distribution of the duration of acute HIV-1 disease is shown in figure 1. The average duration of acute HIV-1 disease was 24.8 days for homosexual men and 26.0 days for other patients ($P = .34$). There was no significant difference in the duration between men (24.6 days) and women (32.5 days) ($P = .13$). The duration of acute HIV-1 disease stratified by age is reported in table 2; there was no difference according to age ($P = .8$). Forty-six patients (21%) were hospitalized. Tables 3 and 4 show the frequency and duration of clinical features.

If we define the classical clinical triad of MLI to be fever (temperature of ≥38°C), sore throat or pharyngitis, and cervical

Table 2. Duration of acute HIV-1 disease stratified by age for 218 patients.

Age (y) at onset of acute HIV-1 disease (no. of patients)	Duration of acute HIV-1 disease (d)*	
	Mean (±SD)	Median (range)
≤24 (49)	26.5 (19.9)	23 (4–76)
25–29 (51)	22.2 (25.9)	17 (4–184)
30–34 (66)	25.1 (19.3)	19 (3–94)
35–39 (25)	24.8 (18.0)	21 (5–82)
≥40 (27)	28.7 (28.6)	20 (5–109)

* The difference in the mean duration according to age was not significant (one-way analysis of variance; $P = .80$).

Table 3. Frequency and duration of signs and symptoms reported for ≥5% of 218 patients at the time of acute HIV-1 disease.

Percentage of patients, sign or symptom	No. (%) of patients	Average duration in d (no. of patients)	Median duration in d (range)
>50%			
Fever (temperature of ≥38°C)	168 (77.1)	16.9 (162)	14.0 (3.0–184.0)
Lethargy	143 (65.6)	23.7 (139)	18.0 (1.0–184.0)
Cutaneous rash	123 (56.4)	15.0 (117)	11.0 (1.0–73.0)
Myalgia	119 (54.6)	17.7 (112)	11.0 (2.0–184.0)
Headache	111 (50.9)	25.8 (108)	13.0 (2.0–continuing*)
>25%–50%			
Pharyngitis or sore throat	96 (44.0)	12.2 (90)	8.0 (1.0–51.0)
Cervical adenopathy	85 (39.0)	15.1 (8)	12.0 (3.0–32.0)
Arthralgia	67 (30.7)	22.6 (64)	15.0 (3.0–184.0)
Oral ulcer	63 (28.9)	13.4 (63)	8.0 (1.0–85.0)
Odynophagia	61 (28.0)	16.3 (58)	14.0 (2.0–48.0)
5%–25%			
Axillary adenopathy	53 (24.3)	164.1 (6)	13.5 (1.0–continuing*)
Weight loss	52 (23.9)	29.0 (49)	19.0 (3.0–continuing*)
Nausea	52 (23.9)	17.8 (50)	14.0 (2.0–109.0)
Diarrhea	50 (22.9)	12.5 (47)	8.0 (1.0–39.0)
Night sweats	48 (22.0)	14.8 (45)	10.0 (3.0–57.0)
Cough	48 (22.0)	18.4 (48)	12.5 (2.0–184.0)
Anorexia	46 (21.1)	14.6 (44)	10.0 (2.0–68.0)
Inguinal adenopathy	44 (20.2)	8.5 (2)	8.5 (7.0–10.0)
Abdominal pain	42 (19.3)	15.1 (40)	12.0 (1.0–73.0)
Oral candidiasis	37 (17.0)	10.4 (34)	7.5 (1.0–34.0)
Vomiting	27 (12.4)	9.8 (27)	10.0 (1.0–31.0)
Photophobia	26 (11.9)	11.2 (25)	10.0 (2.0–39.0)
Sore eyes	25 (11.5)	13.2 (24)	11.5 (3.0–36.0)
Genital ulcer	15 (6.9)	13.5 (15)	12.0 (3.0–35.0)
Tonsillitis	15 (6.9)	13.3 (13)	10.0 (1.0–41.0)
Depression	14 (6.4)	22.8 (9)	7.0 (3.0–76.0)
Dizziness	12 (5.5)	10.7 (10)	9.5 (2.0–26.0)

* The treating physician considered that the sign or symptom became a chronic feature.

adenopathy [20], 34 patients (15.6%) presented with this clinical picture. Only 26 patients (12%) had an MLI if lethargy was included in the definition. Twenty-one patients (10%) had none of these features.

Of the 60 patients with fever but no other MLI features, 31 (52%) had fever plus headache, 15 (25%) had fever plus oral ulcer, 15 (25%) had fever plus abdominal pain, and 10 (17%) had fever plus diarrhea. A meningitis-like syndrome (defined as fever, headache, and stiff neck) occurred in 20 patients (9.2%).

By contrast, fever was not described in 50 patients (23%). In these 50 patients, the most frequent clinical features were sore throat or pharyngitis (23 [46%]), lethargy (22 [44%]), myalgia (18 [36%]), cutaneous rash (17 [34%]), headache (17 [34%]), cervical adenopathy (16 [32%]), oral ulcer (10 [20%]), cough (10 [20%]), and arthralgia (10 [20%]).

There were nine patients infected with zidovudine-resistant (mutant) HIV-1, and two patients were infected with a mixture of both wild-type and mutant strains; 88 patients were infected with a wild-type strain (total number of analyzed cases, 99). For the 11 patients infected only by a wild-type strain, the

mean duration of acute HIV-1 disease was 21.0 days compared with 26.9 days for the 88 patients infected with a mutant or mutant and wild-type strains (P = .48). Infections with HIV-1 variants (mutant strain or mutant and wild-type strains) occurred in 2 patients in 1990, in 3 in 1992, in 4 in 1993, and in 2 in 1994 (until 30 June). The frequency of clinical features was not significantly related to infection with zidovudine-resistant HIV-1 (mutant strain or mutant and wild-type strains). The number of patients was too small to analyze further differences in acute HIV-1 disease between the 11 patients infected with a mutant strain or mutant and wild-type strains and the 88 infected only by a wild-type strain.

Discussion

The purpose of this descriptive study was to investigate extensively the clinical features reported at the time of acute HIV-1 disease in a large cohort of patients. A potential limitation of the study was that the patients differed in terms of risk factors for HIV-1 infection: 91% of the patients in Australia were homosexual men compared with 54% of the patients in

Table 4. Frequency and duration of signs and symptoms reported for <5% of 218 patients at the time of acute HIV-1 disease.

Sign or symptom	No. (%) of patients	Average duration in d (no. of patients)	Median duration in d (range)
Sputum production	10 (4.6)	9.8 (8)	7.0 (3.0–23.0)
Occipital adenopathy	10 (4.6)	NA (NA)	NA (NA)
Gingivitis	10 (4.6)	8.1 (10)	7.0 (3.0–22.0)
Splenomegaly	10 (4.6)	17.8 (7)	8.0 (2.0–48.0)
Irritability	8 (3.7)	25.3 (6)	24.0 (12.0–42.0)
Peripheral neuropathy	8 (3.7)	74.8 (6)	32.0 (13.0–continuing*)
Epitrochlear adenopathy	7 (3.2)	NA (NA)	NA (NA)
Thoracic pain	7 (3.2)	9.4 (7)	7.0 (2.0–27.0)
Hepatomegaly	7 (3.2)	7.7 (3)	4.0 (2.0–16.0)
Supraclavicular adenopathy	6 (2.8)	NA (NA)	NA (NA)
Dysuria or hematuria	6 (2.8)	4.8 (5)	6.0 (3.0–6.0)
Back pain	5 (2.3)	8.0 (5)	7.0 (2.0–16.0)
Disorientation or confusion	5 (2.3)	9.8 (4)	10.5 (3.0–15.0)
Conjunctivitis	4 (1.8)	4.5 (4)	4.0 (3.0–7.0)
Esophagitis	4 (1.8)	8.3 (3)	8.0 (8.0–9.0)
Encephalitis	3 (1.4)	9.6 (3)	10.0 (3.0–16.0)
Anal ulcer	3 (1.4)	NA (NA)	NA (NA)
Psychosis	2 (0.9)	NA (NA)	NA (NA)

NOTE.　NA = not available.
* The treating physician considered that the sign or symptom became a chronic feature.

Europe (which also created an imbalance in the sex ratio). We decided to include patients of both sexes with different risk factors to facilitate the use of our results by physicians who work with populations in whom HIV-1 infection does not occur almost exclusively in one risk group. Until now, all previous studies except two [7, 15] have been limited to one risk population—homosexual and/or bisexual men. Physicians' experience with acute HIV-1 disease may have affected the accuracy of the diagnosis, but this circumstance was probably of limited impact, because clinicians had reached similar levels of clinical expertise in Australia and Europe when the cohorts were started.

Some symptoms and signs overlaped (i.e., tonsillitis and pharyngitis or sore throat), and the reporting of diagnoses was not completely standardized. For example, in the case of tonsillitis, we have to assume that physicians made this diagnosis when "true" tonsillitis rather than simple pharyngitis was present. In any case, tonsillitis and/or pharyngitis or sore throat occurred in 100 patients (46%), thus confirming the frequent involvement of the oral cavity during acute HIV-1 illness.

A description as complete as possible of acute HIV-1 disease gives physicians an understanding of the wide range of diagnostic clinical features that could lead to early therapeutic intervention [7, 8]. The mean and median durations of acute HIV-1 disease were similar to those previously reported [14–16]; for the first time, we report the absence of a difference in the duration by gender, age, and risk groups. Because sicker patients are more likely to be enrolled in the cohorts at the time of acute HIV-1 disease, the clinical description may have been biased toward more severe disease. Nevertheless, the duration

of some signs and symptoms was only a few days, which suggests that mild acute HIV-1 disease was represented in our study.

A possible recall bias may be present for patients enrolled in the study according to biological inclusion criterion 3. To quantify this possible bias, we performed an additional frequency analysis restricted to 153 patients for whom the time relation between symptoms and acute HIV-1 illness was the strongest (criteria 1 and 2). Among this population, we observed an average increase of 3.7% in the frequency of each sign or symptom, a finding suggesting that the analysis performed on the whole sample could not have been very biased.

Although MLI is the major clinical syndrome described in 50% to 70% of patients with acute HIV-1 disease [5, 14, 16] and although MLI is emphasized in textbooks [21, 22], some atypical presentations have occurred, and they have been reported separately [23–25]. The systematic description appearing in this study yields a wide spectrum of clinical features of the disease and a relative frequency of an MLI-type presentation that is low compared with that of less typical presentations. Thus, if the definition of acute HIV-1 disease as an MLI was helpful at the beginning of the AIDS epidemic and is still used [10, 12, 13], our results suggest that the definition of acute HIV-1 disease should be broadened.

When MLI is absent, fever associated with diarrhea, a cutaneous rash, or headaches prompts the diagnosis, especially in the presence of mucosal ulcers. However, in nearly 25% of cases, fever is not reported, but a diagnosis may still be made by eliciting recent risk behavior followed by nonspecific clinical features of illness. Hence, when an acute infectious disease or

an unusual dermatologic condition is noted, practitioners should consider the possibility of acute HIV-1 infection. To do this rigorously, one needs to know how frequently the main signs and symptoms of acute HIV-1 disease occur in patients who do not have acute HIV-1 disease. Our study cannot provide this information, but clinical experience can nonetheless be useful.

The more severe features reported during acute HIV-1 disease were neurological and gastrointestinal. The frequency of the meningitis-like syndrome, peripheral neuropathy, confusion, and encephalitis was similar to that reported in a French study [26] and confirmed the early tropism of HIV for the CNS [27]. Oral candidiasis was observed frequently, and esophagitis was seen more rarely; both conditions are probably related to transient depletion and dysfunction of CD4$^+$ cells.

Analysis of each reported symptom or sign by using a standard questionnaire had the advantage of a greater uniformity of data collection and perhaps a greater validity compared with analysis of pooled data from different clinical studies. For example, in a review of studies of pooled data, Niu et al. [5] reported that fever occurred in 96% of their patients (compared with 77.1% of our patients) and that headache was present in 32% of their patients (compared with 50.9% of our patients); oral ulcers were not reported (whereas they were present in 28.9% of our patients).

We did not find a difference in the duration of acute infection with a zidovudine-resistant strain, thus suggesting that primary infection with an HIV strain with a mutation at codon 215 does not necessarily itself induce a more aggressive initial infection. One previous report [28] cited the development of severe immunodeficiency in a patient after deliberate injection of blood containing a mixture of HIV-1 strains. In this case, it is difficult to assess the relative contributions of inoculum size vs. viral characteristics to early immunodeficiency.

In conclusion, patients with acute HIV-1 disease present with a broad array of symptoms and signs, and <20% have the classical features of an MLI. A febrile syndrome, especially one associated with gastrointestinal or mucocutaneous features, occurring in a person at risk of HIV infection should alert physicians to the possibility of HIV-1 seroconversion. The reasons for the heterogeneous clinical presentation and the relation of those various clinical presentations to the pathogenesis of acute HIV-1 infection and to the response to early treatment remain unclear.

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