Frequency and Spectrum of Unexpected Clinical Manifestations of Primary HIV-1 Infection

Dominique L. Braun,[1,2] Roger D. Kouyos,[1,2] Belinda Balmer,[1] Christina Grube,[1] Rainer Weber,[1] and Huldrych F. Günthard[1,2]

[1]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, and [2]Institute of Medical Virology, University of Zurich, Switzerland

Background. Prospectively and systematically collected data on frequency and spectrum of unexpected clinical manifestations during primary human immunodeficiency virus (HIV) infection (PHI) have not been published.

Methods. We prospectively enrolled 290 patients with documented PHI in the Zurich Primary HIV Infection Study. Typical acute retroviral syndrome (ARS) was defined as fever plus at least 1 symptom or sign typically considered to be associated with ARS; in absence of fever, presence of 2 or more ARS symptoms or signs. Atypical ARS was defined as lack of symptoms or signs, a single symptom or sign only and absence of fever, presence of symptoms or signs that are not considered typically associated with ARS, or occurrence of an opportunistic disease. Time to diagnosis was calculated based on estimated date of infection and first positive HIV test.

Results. We analyzed 290 patients (271 males). PHI manifested with typical ARS in 202 (70%) and with atypical ARS in 88 (30%) patients. Patients with atypical ARS were hospitalized 4 times more often compared with typical ARS (43% vs 11%; $P < .001$). The gastrointestinal tract was the most frequent organ system affected in patients with atypical manifestations. Only in 112 (38%) patients was HIV infection suspected during the first medical attendance. Patients with typical ARS were diagnosed slightly earlier compared with atypical ARS, but this difference was not significant ($P = .3$).

Conclusions. Unexpected clinical presentations occurred in a large fraction of patients with PHI and were associated with substantial morbidity. Universal HIV testing may be mandatory in high-risk groups.

Keywords. primary HIV-1 infection; acute HIV-infection; acute retroviral syndrome; ARS; atypical clinical presentation.

Primary human immunodeficiency virus type 1 (HIV-1) infection (PHI) encompasses the first 3 to 6 months after infection and presents symptomatically in 23% to 92% of newly infected individuals [1–13]. Signs and symptoms that occur during seroconversion are often referred to as acute retroviral syndrome (ARS). However, there is no distinct definition of ARS, and diverse numbers on frequency and a variety of clinical manifestations are reported [11]. Reliable data on the proportion of asymptomatic or oligosymptomatic PHI are lacking since asymptomatic persons usually do not seek medical care. Studies that include an HIV-negative control group may be limited due to a recall bias [5, 10]. The nonspecific and transient nature of symptoms associated with PHI provides a major diagnostic challenge and substantially contributes to ongoing virus transmissions [14]. Early recognition of PHI is therefore important in order to interrupt the transmission chain and maximize the potential benefit of early antiretroviral treatment (ART) [15]. Severe clinical manifestations, including opportunistic diseases, and a broad spectrum of affected organ systems during PHI have been reported (Supplementary Appendix 1). Nevertheless, whether the proportion and the disease pattern of atypical clinical presentation during PHI influence the time to diagnosis has not yet systematically been studied.

We prospectively observed 290 patients with a documented PHI with regard to the infection's clinical

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Correspondence: Dominique L. Braun, MD, University Hospital Zurich, University of Zurich, Division of Infectious Diseases and Hospital Epidemiology, Raemistrasse 100, 8091 Zürich, Switzerland (dominique.braun@usz.ch).

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Table 1. Comparison of Typical Clinical Manifestations of Acute Retroviral Syndrome: Data From Present Study and Data From Published Studies With Different Study Designs

Clinical Manifestation and Laboratory Finding	Present Study, n (%), N = 202		Median Frequency (%) in Published Studies[a]			
			Retrospective,[b] n = 227	Prospective,[c] n = 255	Human Immunodeficiency Virus-Negative,[d] n = 8345	% Range of All Studies
Clinical manifestation						
Fever	178	88	78	48	88	23–100
Malaise/Fatigue	122	60	64	25	65	12–92
Pharyngitis	103	51	48	21	51	2–95
Rash	94	47	38	12	47	4–75
Lymphadenopathy	91	45	36	36	45	7–75
Weight loss	79	39	21	21	39	2–70
Headache	74	37	44	34	37	18–57
Diarrhea	71	35	32	17	35	14–48
Night sweats	68	34	14	9	34	3–48
Myalgia	56	28	46	20	28	14–92
Nausea	53	26	32	19	26	6–67
Arthralgia	44	22	27	21	22	14–92
Cough	33	16	25	14	16	4–45
Vomiting	24	12	32	11	12	3–67
Oral ulcers	24	12	17	9	12	9–30
Neurological symptoms	22	11	12	. . .	11	0–24
Genital ulcers	7	3	3	3	3	3–10
Elevated liver enzymes	124	61	21	. . .	. . .	21–61
Thrombocytopenia	74	37	60	. . .	. . .	37–60

A total of 202 of 290 patients presented with typical acute retroviral syndrome.

[a] References [1–13].

[b] Data from 11 retrospective studies or review articles, as summarized in Supplementary Appendix Table 2.

[c] Data from 5 prospective seroconverter studies with a human immunodeficiency virus (HIV)-negative control group, as shown in Supplementary Appendix Table 3.

[d] Data from 5 prospective studies reporting symptoms from an HIV-negative control group, as shown in Supplementary Appendix Table 4.

presentation. Our aim was to characterize the clinical manifestations of PHI and compare them to those described in the literature, determine the proportion of patients who present with typical or atypical ARS, and determine whether atypical presentation delays diagnosis.

METHODS

Study Design and Definition of Primary HIV-1 Infection

A total of 290 patients with documented PHI were prospectively enrolled between January 2002 and January 2013 into the Zurich Primary HIV Infection Study, which is an open-label, nonrandomized, observational, single-center study (http://clinicaltrials.gov, ID 5 NCT00537966) [16]. The ethics committee of the Canton of Zurich approved the study protocol, and written informed consent was obtained from all patients.

Acute or recent PHI was confirmed in all patients as previously described [16–18]. Acute HIV infection was defined as ARS and negative or indeterminate Western blot in the presence of a positive p24-antigen and/or detectable HIV-1 RNA or as a documented seroconversion with or without symptoms during the past 90 days. Recent infection was defined as possible ARS, positive Western blot and detectable HIV-RNA, and a negative HIV-gp120 avidity or detuned assay or as a documented acute HIV-1 infection but with referral to our center between 90 and 180 days after the estimated date of infection (EDI).

Assessment of Acute Retroviral Syndrome

At the first visit, a detailed history and physical examination were performed and standard laboratory parameters were obtained. Additionally, information on occurrence of an acute illness, a need for invasive procedures, and microbiological findings during PHI were assessed. Patients were actively screened for other sexually transmitted infections (STIs). If patients were referred from an external physician, data from the first external visit were recorded.

Table 2. Baseline Characteristics of 290 Patients With Primary Human Immunodeficiency Virus Infection Presenting With Typical vs Atypical Symptoms of Acute Retroviral Syndrome

					Atypical ARS			
	Total Patients		Typical ARS		Symptomatic		Asymptomatic	
Characteristic	n	% or Range	n	% or Range	n	% or Range	n	% or Range
Number of patients	290	100	202	70	74	25	14	5
Male	271	93	191	95	68	92	12	86
Female	19	7	11	5	6	8	2	14
Age (y)	36	18–70	35	18–60	38	19–70	33	20–51
Human immunodeficiency virus type 1 Subtype B[a]	220	76	163	81	47	64	10	71
Transmission mode								
Men who have sex with men	225	78	161	80	52	70	12	86
Heterosexual	59	20	35	16	22	30	2	14
Intravenous drug users	4	1	4	3	0		0	
Others[b]	2	1	1	1	0		0	
STIs[c]	49	17	37	18	9	12	3	21
Transmitted drug resistance	23	8	13	6	7	9	3	21
Fiebig stages[d]								
I–II	3	1	3	2	0	0	0	0
II–III	48	17	39	19	11	15	0	0
IV–VI	218	75	144	71	60	82	14	100
Viral load $\log_{10}$ RNA	6.6	1.8–8	6.6	2.3–8	6.7	2.7–8	5.1	1.8–5.9
$CD4^+$ cell count, cells/μL	429	75–1255	424	75–1255	431	127–1040	498	326–630
Initial care setting								
Primary care physician	141	49	107	53	32	43	2	14
Hospital	69	24	37	18	28	38	4	29
STI outpatient clinic	42	15	33	16	7	9	2	14
Other[e]	55	19	24	12	5	7	6	43
Unknown	3	1	1	1	2	3	0	000
Required hospitalization	50	17	22	11	38	43	0	0

Abbreviations: ARS, acute retroviral syndrome; STI, sexually transmitted infection.

[a] Other subtypes: CRF01_AE, C, A, F1, G, CRF02_AG, CRF14_BG, A1D, CR 12_BF, D.

[b] One case of a needle stick injury in a medical setting.

[c] Concomitant STIs: syphilis and/or chlamydia and/or gonorrhea and/or genital herpes.

[d] In 21 patients, a Fiebig stage could not be assigned due to missing p24-antigen values.

[e] Other than infectious disease specialist or other institutions (eg, dermatologist, gynecologist, blood donation center).

Estimated Date of Infection and Time to Diagnosis

For each patient, an EDI was determined by taking into account the different patterns of assay reactivities (first positive and last negative HIV test; negative, indeterminate, and positive Western blot; positive p24 antigen), patient's report of unambiguous risk contacts, and timing of onset of ARS symptoms. The detailed algorithm to calculate the EDI was previously published [16–18]. The time to diagnosis was calculated based on the EDI and the date of the first positive HIV screening test.

Definition of Typical and Atypical Acute Retroviral Syndrome

First, we extensively reviewed the literature on reported signs and symptoms associated with PHI (Supplementary Appendices 2–4) [1–6, 8–13]. Based on this literature search, we defined 17 symptoms and signs that we considered typical of ARS (Table 1). Next, we distinguished typical and atypical ARS among our study population. ARS was considered typical in case of documented or reported fever (temperature ≥38°C) plus at least 1 of the symptoms or signs listed in Table 1; in the absence of fever, 2 or more of these symptoms or signs needed to be present. ARS was defined as atypical in cases of lack of any signs or symptoms, a single sign or symptom, an opportunistic disease according to the Centers for Disease Control and Prevention (CDC) classification stage B or C, presence of symptoms or signs not included in Table 1, evidence of unusual clinical manifestations of PHI as described in the literature (Supplementary Appendix 1), or other symptoms or signs. If patients were classified into the group of atypical ARS (eg,

Table 3. Atypical Clinical Presentations in 88 of 290 Patients With a Primary Human Immunodeficiency Virus Infection

Clinical Presentation	N (%)	Acute Infection, n (%)	Mean $CD4^+$ (%)	Mean Viral Load, log_{10}RNA	Inpatient, n (%)
Total	88 (100)	71 (79)	460 (27)	5.1	38 (43)
Opportunistic diseases[a]					
Candida stomatitis/esophagitis[b]	13 (14)	12 (92)	346 (26)	6.7	8 (62)
CMV colitis[c]	1 (1)	. . .	164 (22)	6.5	1 (100)
CMV gastritis	1 (1)	1 (100)	427 (26)	6.1	. . .
CMV hepatitis	2 (2)	2 (100)	432 (24)	6.7	2 (100)
Multisegmental herpes zoster	1(1)	1 (100)	305 (21)	5.4	. . .
Autoimmune thrombocytopenia[d]	1 (1)	1 (100)	165 (24)	6.4	1 (100)
Peripheral polyradiculoneuritis	1 (1)	1 (100)	215 (9)	6.0	. . .
Severe diarrhea >30 d	1 (1)	1 (100)	343 (28)	6.0	2 (50)
Total opportunistic diseases	21 (23)	19 (90)	299 (23)	6.2	14 (67)
Central nervous system					
Severe encephalitis	2 (2)	2 (100)	480 (35)	6.5	2 (100)
Herpes simplex virus 1 meningitis	1 (1)	1 (100)	685 (35)	6.3	1 (100)
Paresis (eg, facio-brachial)	3 (3)	2 (66)	460 (16)	6.8	2 (66)
Prolonged vertigo	1 (1)	1 (100)	222 (33)	6.5	1 (100)
Acute psychiatric disorder	3 (3)	1 (33)	466 (19)	6.5	1 (33)
Distal paresthesias, aphasia	1 (1)	1 (100)	589 (18)	4.8	. . .
Total central nervous system	11 (12)	8 (73)	483 (26)	6.2	7 (64)
Eye					
Herpes keratitis	1 (1)	1 (100)	470 (18)	5.6	. . .
Gastrointestinal tract					
Unilateral or bilateral tonsillitis	6 (7)	4 (66)	364 (29)	6.9	3 (50)
herpes simplex virus type 1 stomatitis/esophagitis/anitis	1 (1)	1 (100)	389 (38)	6.9	1 (100)
Severe gastritis with gastric[c] bleeding	1 (1)	1 (100)	503 (36)	8.0	1 (100)
Diarrhea (only symptom)	1 (1)	1 (100)	602 (34)	3.4	. . .
Acalculous cholecystitis[c]	1 (1)	1 (100)	643 (29)	7.0	1 (100)
Appendicitis-like illness[c]	1 (1)	1 (100)	840 (35)	4.2	1 (100)
Anal abscess with *Enterococcus faecium*[e,c]	1 (1)	1 (100)	277 (18)	6.2	1 (100)
Anitis	1 (1)	. . .	378 (25)	6.7	. . .
Total gastrointestinal symptoms	13 (14)	10 (77)	499 (31)	6.1	8 (62)
Respiratory tract					
Pneumonia	3 (3)	3 (100)	260 (15)	6.1	1 (33)
Upper respiratory tract infection	2 (2)	2 (100)	257 (25)	5.0	. . .
Total respiratory symptoms	5 (6)	5 (100)	258 (20)	5.6	1 (20)
Heart					
Acute atrial fibrillation	1 (1)	1 (100)	329 (17)	6.6	. . .
Urogenital tract					
Acute renal failure	2 (2)	1 (100)	355 (43)	5.0	2 (100)
Nonbacterial prostatitis	1 (1)	. . .	990 (38)	3.8	. . .
Epididymitis[c]	1 (1)	1 (100)	196 (21)	3.7	1 (100)
Total urogenital symptoms	3 (3)	2 (66)	514 (34)	4.1	3 (66)
Skin and soft tissue					
Impetigo contagiosa	1 (1)	1 (100)	432 (35)	5.4	. . .
Soft tissue infection	3 (3)	3 (100)	664 (31)	4.5	2 (100)
Hair loss	1 (1)	. . .	698 (40)	4.9	. . .
Severe dermatitis	3 (3)	2 (75)	774 (26)	5.9	. . .
Total, skin/soft tissue symptoms	8 (9)	6 (75)	546 (29)	5.2	2 (25)

Table 3 continued.

Clinical Presentation	N (%)	Acute Infection, n (%)	Mean $CD4^+$ (%)	Mean Viral Load, log_{10}RNA	Inpatient, n (%)
Blood system					
Severe pancytopenia[f]	3 (3)	3 (100)	329 (29)	6.7	3 (100)
Thrombophlebitis Vena brachiocephalica	1 (1)	1 (100)	127 (12)	5.8	. . .
Total hematologic findings	5 (6)	5 (100)	338 (20)	5.6	3 (80)
Constitutional symptoms					
Weight loss or night sweats	7 (8)	7 (100)	476 (26)	5.2	. . .
Symptomatic atypical PHI	74 (85)	64 (71)	421 (24)	5.0	38 (43)
Asymptomatic atypical PHI	14 (15)	7 (8)	499 (30)	4.4	. . .

Abbreviations: CMV, cytomegalovirus; PHI, primary human immunodeficiency virus infection.

[a] According to the Centers for Disease Control and Prevention classification state B or C.

[b] In 2 cases, together with severe neurological symptoms.

[c] Surgical intervention required (eg, laparotomy, laparoscopy, rectostomy).

[d] Together with generalized herpes simplex 1 skin infection.

[e] Leading to rectostomy; in addition, bilateral *Pseudomonas aeruginosa* pneumonia, arthritis of the left knee, acute renal insufficiency.

[f] In 1 case, together with *Enterococcus faecalis* bacteremia, pneumonia, skin abscesses, retinal hemorrhagia.

manifesting with cytomegalovirus [CMV] colitis), their accompanying symptoms or signs (eg, fever, diarrhea) were not additionally counted as typical ARS symptoms. In patients with atypical ARS who presented with multiple diseases, classification into the affected organ system was based on their primary clinical symptom or sign and they were counted only once. If patients presented with an opportunistic disease plus another atypical manifestation of PHI, their case was counted as opportunistic disease and not classified within 1 of the different organ systems.

Statistical Analysis

We used logistic regression to test whether typical vs atypical ARS was associated with the initial place of presentation (hospital vs ambulatory healthcare institutions) and to test whether it was associated with subsequent hospitalization. Since time to diagnosis (ie, time from the EDI to the first positive HIV test) was not normally distributed, we used the Kruskal–Wallis test to determine whether time to diagnosis differed among patients with different types of presentation (ie, typical ARS, symptomatic atypical ARS, and asymptomatic presentation). Finally, we used the Wilcoxon rank-sum test to determine whether the time to diagnosis differed between patients who initially presented to an STI outpatient clinic and patients diagnosed at other institutions.

RESULTS

Patient Characteristics

We analyzed 290 individuals with a documented PHI, including 271 (93%) males. The baseline characteristics are shown in Figure 1 and summarized in Table 2. A total of 202 (70%) patients were classified in the group of typical ARS and 88 (30%) in the group of atypical ARS. In the latter group, 74 (25%) presented with atypical signs and symptoms of ARS, and 14 (5%) were asymptomatic (Table 3). The majority of patients (49%) first consulted their primary care physician during the phase of seroconversion (Table 2). Patients with an atypical ARS presented more frequently to a hospital compared with patients with typical ARS ($P < .001$; odds ratio [OR], 2.7; 95% confidence interval [CI], 1.5, 4.5). Fifty (17%) of the 290 patients required hospitalization.

First Diagnosis During the Phase of Seroconversion

The first established diagnoses, when patients initially presented with symptoms or signs of PHI, are summarized in Table 4. HIV infection was suspected during the first medical attendance in only 112 (38%) patients.

Atypical Presentation of Primary HIV-1 Infection

Of all 290 patients, 88 (30%) had an atypical ARS manifestation (Table 3). Of these, 14 (16%) were completely asymptomatic and were diagnosed by physician-initiated HIV screening or testing requested by the patient. The remaining 74 (84%) patients presented symptomatically with a diverse pattern of symptoms and signs (Table 3). The gastrointestinal (GI) tract and the central nervous system (CNS) were the most frequently affected organ systems. The opportunistic diseases and the atypical manifestations which occurred during PHI and affected different organ systems are specified in the following list:

Opportunistic diseases

Twenty-one of 88 (24%) patients with atypical ARS presented with an HIV-associated CDC stage B or C illness. *Candida* stomatitis and/or esophagitis were the most frequent opportunistic diseases; 6 patients presented with CMV disease, including 2 with histologically proven colitis and gastritis and 2 with

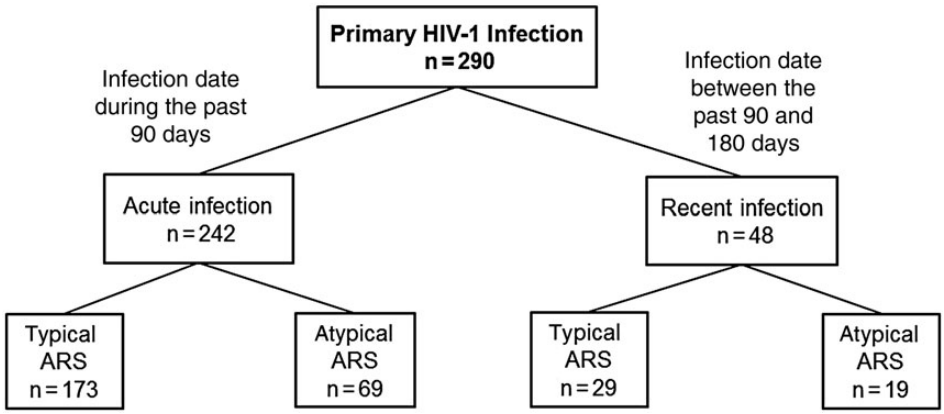

Figure 1. Classification of 290 patients with primary human immunodeficiency virus infection according to their infection and acute retroviral syndrome (ARS) state. Abbreviation: HIV-1, human immunodeficiency virus type 1.

hepatitis and documented CMV seroconversion and viremia. Other opportunistic diseases included multidermal herpes zoster, HIV-associated autoimmune thrombocytopenia, peripheral demyelinating polyradiculoneuritis, and diarrhea for several weeks with wasting syndrome.

Central nervous system

The most severe CNS manifestations included 2 cases with fulminant encephalitis, leading to a stay in the intensive care unit for 1 patient. Other CNS manifestations were facial and occulomotor nerve palsy; prolonged vertigo, leading to an otorhinolaryngology assessment (in the absence of syphilis); acute psychiatric disorders (eg, psychosis, severe depression); and herpes simplex virus type 1 (HSV-1) meningitis.

Ocular

One patient presented with HSV-1 keratitis of the right eye during PHI.

Table 4. Initial Diagnosis of First Attended Healthcare Provider or Reason for Human Immunodeficiency Virus (HIV) Test at Time Point of HIV Seroconversion

Suspected Diagnosis	Frequency (%)
Acute retroviral syndrome	112 (38)
Viral infection other than HIV (eg, mononucleosis infectiosa)	49 (17)
Routine HIV test	35 (12)
Bacterial infection (eg, Streptococcal pharyngitis)	16 (6)
Gastroenteritis	11 (4)
Sexually transmitted infection (eg, syphilis)	10 (3)
Other[a]	55 (19)

Abbreviation: HIV, human immunodeficiency virus.

[a] Includes a variety of diseases (eg, infective endocarditis, diverticulitis, appendicitis, malignant lymphoma, Lyme disease). No data were available for 2 patients.

GI tract

Unilateral or bilateral tonsillitis, in the absence of other STIs, was present in 6 patients. In all of these patients, the first suspected diagnosis was a group A streptococcal tonsillitis, and antibiotics were prescribed. Severe morbidity in other patients was due to necrotizing esophagitis, HSV-1 panmucositis, gastric ulcer that caused anemic bleeding and required surgical intervention, acalculous cholecystitis, and an anal abscess due to *Enterococcus faecium*. The patient with anal abscess was a previously healthy 28-year-old man who has sex with men (MSM) and presented with concomitant *Pseudomonas aeruginosa* sepsis, bilateral pneumonia, septic knee arthritis, and *Candida* esophagitis. He required several surgical interventions and a descendostomy for 3 months. One patient presented with an appendicitis-like illness that resulted in explorative laparotomy.

Respiratory tract

In 3 patients, pneumonia (viral) was the main clinical finding during PHI, without evidence of a bacterial etiology. Two of these patients were hospitalized due to severe respiratory distress.

Heart

A 45-year-old man reported new onset of chest pain and dyspnea. The electrocardiogram at the time of admission showed a new-onset atrial fibrillation, perhaps triggered by the acute HIV infection. Further investigations revealed no underlying cardiac diseases (eg, coronary heart disease, arterial hypertension).

Urogenital tract

Manifestations included 2 patients with acute renal failure, probably caused by a toxic effect of HIV that led to tubulopathy, a prerenal component, and concomitant intake of nonsteroidal antiinflammatory drugs. One patient presented with acute

epididymitis requiring surgical intervention, and 1 presented with acute prostatitis.

Skin and soft tissue

Eight patients reported new-onset skin and soft tissue manifestations as primary clinical signs during PHI. One patient experienced severe acute hair loss.

Hematologic system

A 63-year-old man presented with pancytopenia, *Enterococcus faecalis* septicemia, abscess of the right hand, and retinal bleeding. One patient suffered from acute Mondor disease (ie, thrombophlebitis of the superficial veins of the breast and anterior chest wall), which resolved after starting early ART.

Constitutional symptoms

Seven patients reported either weight loss or night sweats during the time of seroconversion.

Course of Atypical PHI and Outcome

Patients with atypical ARS (n = 88) were hospitalized 4 times more often compared with patients with typical ARS (n = 202; 43% vs 11%; $P < .001$; OR, 4.4; 95% CI, 2.4, 8.3). There was no PHI-associated death in our cohort. An invasive diagnostic or therapeutic procedure was required in 6 (6.5%) of the 88 patients with atypical ARS. One patient underwent hemicolectomy following colonic perforation associated with CMV enteritis, 1 patient with anemic gastric bleeding required urgent gastroscopy with clipping, 2 patients who presented with acute abdominal pain during seroconversion underwent explorative laparotomy, 1 patient with anal abscess required a transient ileostomy, and 1 patient with epididymitis underwent a surgical epididymectomy.

Time to Diagnosis in Patients With Atypical Primary HIV-1 Infection

We determined the time interval between the EDI and the first positive HIV test in patients with typical ARS, atypical symptomatic ARS, and asymptomatic PHI. We found that atypical presentation did not lead to a significant delay in diagnosis. Median time to first positive test among asymptomatic newly infected persons was 42 days (95% bootstrap confidence interval, 18.4, 65.6); among patients with atypical symptomatic ARS, 32 days (25.8, 38.2); and among patients with typical ARS, 29 days (24.8, 33.2; Kruskal–Wallis test for differences between groups, $P = .3$). Patients who initially presented to an STI outpatient clinic were diagnosed significantly earlier compared with patients admitted to a hospital or primary care physician. Median time to first positive test among patients attending an STI outpatient clinic was 21 days (95% bootstrap confidence interval, 18, 31); among patients presenting to a hospital, 30 days (20, 61); and among patients presenting to their primary care physician, 33 days (22, 53; Wilcoxon rank-sum test for differences between STI outpatient clinic and other groups, $P < .0002$).

DISCUSSION

In this prospective, single-center, cohort study that included 290 patients with a well-documented PHI, we found that one third of patients presented with atypical clinical manifestation during HIV seroconversion. Almost half of patients with atypical presentation (43%) were severely ill and required inpatient treatment, which also had a potential economic impact. Only in 112 (38%) patients was acute HIV infection suspected by physicians at the first visit. Surprisingly, clinical presentation with atypical ARS did not significantly delay PHI diagnosis.

The proportion and clinical spectrum of unusual clinical presentations of PHI have not prospectively and systematically been studied and published in the literature, and there is no consensus when clinical manifestations of PHI are considered atypical. We therefore classified typical and atypical PHI based on published data that we then compared with the results of the present work. An unexpectedly large number of patients (30%) fulfilled the criteria for atypical PHI. To date, more than 30 cases describing atypical clinical manifestations during PHI have been published, including a broad spectrum of diseases and affected organ systems (Supplementary Appendix 1). Our review of the literature showed that, similar to our study, most of the anecdotal atypical cases affected the GI tract or the CNS (Supplementary Appendix 1). An unfavorable outcome is reported in approximately half of the atypical PHI cases. The high prevalence of GI tract involvement in our cohort may partially be explained by the route of HIV transmission—the majority of our patients (78%) are MSM. Studies in humans and animals have shown that after rectogenital infection, HIV preferentially infects resting $CD4^+$ cells from the gut-associated lymphoid tissue, leading to a massive cytokine-mediated local inflammation [19]. This mechanism may result in either direct cytotoxic-related tissue damage (eg, HIV-associated colitis) or local reactivation of other viral infections (eg, CMV colitis). Furthermore, a recent publication reported that HIV invades the CNS as early as 8 days after transmission, causing intrathecal immune activation and inflammation, which led to clinical manifestations in a substantial number of patients [20].

We did not find that atypical manifestations delayed HIV diagnosis significantly, although patients with typical ARS were diagnosed a few days earlier than those with atypical PHI. This finding may be explained by the often severe clinical presentation of patients, which possibly led them to associate their HIV transmission risk with the subsequent illness and to request testing; the large proportion of MSM who possibly requested early testing; awareness of past risk behavior, which also led asymptomatic persons to request testing; and the high

variability of the recognition of typical ARS, which may have diminished or eliminated the power to detect a deleterious effect of atypical ARS, in part, due to the relatively small number of total events as well as atypical presentations.

Although clinical manifestations of ARS have repeatedly been described, PHI is still often missed. A recent review on the utility of clinical evaluation to detect PHI concluded that the assessment of symptoms and signs might be unreliable for diagnosis [21]. In our cohort, PHI was initially suspected in only 112 of the 290 patients (38%) by primary care physicians or at hospital emergency units. Healthcare providers and patients should be aware of the substantial proportion of unusual manifestations of acute HIV infection. However, physicians should search for other underlying diseases in cases where signs and symptoms may be not clearly attributable to HIV itself so as to not miss diseases that require specific treatment.

Although the majority of our patients (94%) presented symptomatically during PHI, we assume that this number is biased for many reasons. First, asymptomatic younger persons usually do not routinely attend healthcare institutions, and HIV infection therefore will only be detected if sexually active persons are aware of their risks and request testing. Second, our cohort did not prospectively include and observe an HIV-negative control group. In a prospective observational study that included individuals in East Africa and Thailand at high risk for HIV infection, O'Connell and colleagues reported that more than 50% of all participants enrolled into the study presented asymptomatically at the time point of seroconversion [22]. Thus, it is possible that the proportion of patients with atypical (ie, asymptomatic) ARS was considerably underestimated in our study. However, published data on ARS symptoms from studies that included an HIV-negative control group are potentially limited due to an inherent recall bias (ie, patients do not remember transient or preceding nonspecific symptoms in the previous 6 months and, furthermore, would probably not be enrolled in a study if they had no risk at all). Third, common symptoms or signs of PHI also occur in many other clinical situations apart from PHI, for example, other viral infections, and may be misinterpreted. Symptoms observed among HIV-negative "control" persons in prospective HIV seroconverter studies are frequent and include fever or pharyngitis due to etiologies other than HIV in up to 20% or a preceding acute illness in up to 40% in the previous 6 months [3–6, 10].

The strengths of our study are the prospective design, the large number of observed seroconverters, the systematic documentation by a stable and experienced study team, and the strict use of clinical and laboratory criteria to define PHI. However, limitations include that the definition used to classify atypical PHI is not formally validated. Since there was no broadly used definition of ARS, we had to propose de novo criteria, which we based on an extensive literature search. However, a coincidental comorbidity during PHI cannot be ruled out in some cases. One additional limitation is the lack of information of how many of the HIV tests were ordered by the physicians for suspected HIV infection with respective to how many tests were requested by the patients themselves. This information would be helpful to determine whether it would be more effective in terms of early diagnosis to inform physicians on potential symptoms and signs of PHI or whether the focus should be on advocating testing in populations at risk. Last, our cohort included only 1 case infected by intravenous drug use, whereas 99% were infected by sexual routes. Some studies reported a lower frequency of ARS symptoms among intravenous drug users. However, whether this is a true finding or whether PHI symptoms were observed less frequently because of other substantial comorbidities in intravenous drug users remains unknown [7].

In conclusion, unexpected atypical presentations and opportunistic diseases occur in a substantial proportion of patients with PHI, often causing severe disease. Our findings warrant general HIV testing in populations at risk.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Authors' contribution statement. H. F. G. conceptualized, designed, and supervised the study. Data acquisition was done by D. L. B., R. D. K., B. B., C. G., and H. F. G. Statistical analysis was performed by R. K. All investigators contributed to data collection and interpretation, reviewed drafts of the manuscript, and approved the final manuscript.

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