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Prevalence, clinical characteristics and outcome of severe primary HIV-1 infection: A prospective cohort study

David Nicolás[a,1], Antoni Suárez[a,1], Juan Ambrosioni[a], Christian Manzardo[a], Carmen Ligero[a], Josep Costa[b], Emma Fernández[a], M. Ángeles Marcos[c], Montserrat Plana[d], María Mar Mosquera[c], Sonsoles Sánchez-Palomino[d], Jose M. Gatell[a], José M. Miró[a,*], the Hospital Clinic PHI investigators

[a] Infectious Diseases Service, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain
[b] Microbiology Service, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain
[c] Microbiology Service, Hospital Clinic, University of Barcelona, Institute for Global Health, (ISGlobal), Barcelona, Spain
[d] Retrovirology and Viral Immunopathology Laboratory, AIDS Research Group, IDIBAPS, Hospital Clínic, University of Barcelona, Spain

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ABSTRACT

Background: Severe cases of primary HIV infection have been described in patients presenting with neurological involvement, AIDS defining events or other life-threatening events. These severe forms have not been fully studied.
Objectives: To determine the prevalence and characteristics of severe PHI in a hospital-based cohort of primary HIV infection, and the response to the early initiation of antiretroviral therapy (ART) at 12 months.
Methods: Every patient with PHI attending Hospital Clínic of Barcelona (1997–2015) was evaluated. Severe PHI was defined using clinical, analytical and immunological criteria. Chi-squared test was used for categorical variables and Student's t-test for quantitative variables.
Results: 33% of 224 PHI patients (95% CI: 26.84%–39.16%) had a severe PHI. These patients had more symptoms, abnormal analytical parameters and hospital admissions. The severe PHI group had a significantly higher viral load although no differences were observed at 12 months in terms of viral suppression or CD4 count recovery. None died during PHI.
Conclusions: Up to one third of patients in our cohort presented with a severe PHI, which was associated with higher hospitalization rates and higher plasma HIV RNA viral load. However, severe forms were not associated to a worse clinical, immunological or virological outcome at 12 months.

Introduction

Primary HIV-1 infection (PHI) usually presents with non-specific symptoms in a variable proportion of patients, ranging from 40% to 90% according to the study and the setting (hospital based or community based cohorts) (Sued et al., 2006; Braun et al., 2015). Typical HIV symptoms are mild and resemble a mononucleosis-like syndrome, with fever, asthenia, pharyngitis, rash, and lymphadenopathies being the most frequent. However, some patients present more severe forms of infection such as opportunistic infections (Braun et al., 2015), neurological involvement (Ambrosioni et al., 2017) and other serious conditions. Although many individual cases have been reported, a systematic study and definition of the incidence and characteristics of severe PHI is lacking. Some features during PHI have been associated with disease progression (AIDS/death). These events were: a low CD4 count at diagnosis, some pre-defined severe symptoms and central nervous system involvement (Lodi et al., 2013). In 2014 an Acute HIV Severity Index based on these criteria was proposed by Braun et al (Braun et al., 2014). In recent years early treatment initiation in every HIV-diagnosed patient has

* Corresponding author at: Infectious Diseases Service, Hospital Clínic, Helios Building, Desk no. 26. Villarroel, 170. 08036 Barcelona, Spain.
E-mail addresses: dnicolas@clinic.cat (D. Nicolás), antonisuarez97@gmail.com (A. Suárez), ambrosioni@clinic.cat (J. Ambrosioni), cmanzardo@gss.scs.es (C. Manzardo), mligero@clinic.cat (C. Ligero), jcostac@clinic.cat (J. Costa), efernang@clinic.cat (E. Fernández), mmarcos@clinic.cat (M. Á. Marcos), mplana@clinic.cat (M. Plana), mdmosquera@clinic.cat (M.M. Mosquera), ssanchez@clinic.cat (S. Sánchez-Palomino), josemgatell@gmail.com (J.M. Gatell), jmmiro@ub.edu (J.M. Miró).
[1] Equivalent merits.

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become the standard of care and has been implemented as a recommendation in all international guidelines (INSIGHT START Study Group et al., 2015; European AIDS Clinical Society, 2017; Günthard et al., 2016).

The aim of this study was to describe the prevalence and the characteristics of patients with severe PHI in a large hospital-based single center. We also aim to evaluate the differences in immunological and virological outcome at 12 months between both severe and non-severe groups.

Methods

The 'Hospital Clinic Acute/Recent HIV Infection Cohort' comprises 346 consecutive patients between April 1997 and December 2015. Hospital Clinic is a public, tertiary teaching hospital which serves 560,000 people in the metropolitan area of Barcelona. The catchment area and the patient recruitment have remained unchanged during the study period. Approximately 5,000 HIV-positive patients are on active follow up and more than 90% are on antiretroviral therapy (ART). For the purpose of this study, only the patients with confirmed PHI with less than 90 days were selected (N = 224, Fiebig I-V) defined by one of the following at diagnosis: a negative ELISA with a detectable viral load or a positive p24 antigen or a positive ELISA with a negative, indeterminate or incomplete (lacking p31 band) Western blot (Fiebig et al., 2003). Patients were actively questioned and examined for clinical signs and symptoms of seroconversion at the first clinical visit. Clinical follow up and blood samples, including viral subtype and tropism, were obtained at diagnosis and at the time of ART initiation, and every six months thereafter (Sued et al., 2006; Nicolás et al., 2018).

Study definitions

PHI was defined as a confirmed infection of less than 90 days according to the different Fiebig stages, defined by one of the following: a negative ELISA with a detectable viral load or a positive p24 antigen or a positive ELISA with a negative, an indeterminate or incomplete Western blot (Fiebig stages I to V) (Fiebig et al., 2003). Severe PHI was defined as those patients presenting at least one clinical, analytical or immunological severity criterion based on previously published works (Lodi et al., 2013; Braun et al., 2014). Clinical severity was defined as presenting a B or C event of the CDC classification (Schneider et al., 2008), neurological manifestations or non-hepatotropic virus related hepatitis (determined as presenting analytical levels of either aspartate aminotransferase/ASAT or alanine aminotransferase/ALAT at diagnosis 10 times higher than the upper normal values range with absence of active hepatitis A, hepatitis B virus or hepatitis C virus infection markers). Analytical severity was defined as severe thrombocytopenia (platelets below 100×109/L, according to the WHO classification), and immunological severity was established with CD4 counts below 350 cells/mm^3 at the moment of the diagnosis (Figure 1). Comorbidities were determined according to the Charlson Comorbidity Index (Charlson et al., 1987).

Statistical analysis

Chi-squared test was used for dichotomous and nominal variables and Student's t-test for continuous quantitative variables. Finally, a comparison of the evolution of immunologic and virologic parameters during one year in patients who started early ART was made between severe and non-severe groups. IBM SPSS program (version 19.0) was used to carry out the statistical analyses.

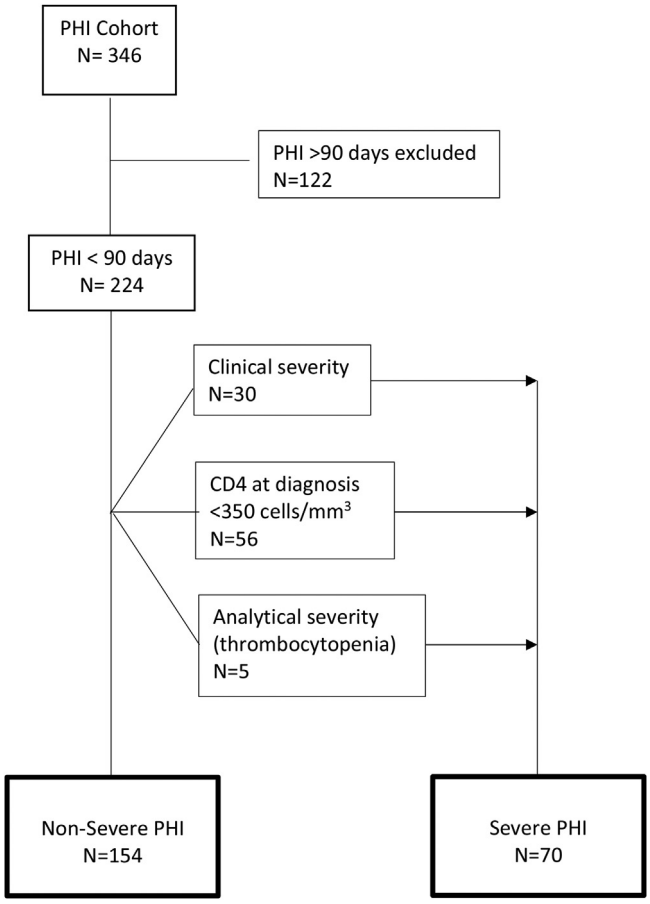


Figure 1. Flow chart representing the inclusion of patients in the severe and non-severe groups.

Results

Main epidemiological characteristics of PHI cohort

A total of 224 patients presented with a PHI of less than 90 days between 1997 and 2015 and, of them, 74 (33%) (95% CI: 26.84-39.16) presented with a severe form of PHI. Baseline characteristics are shown in Table 1. The cohort was composed of 210 (93.8%) males and 14 (6.3%) females, with a median age at diagnosis of 35 years (interquartile range 29-39). At diagnosis, 38 (17.0%) patients were identified as Fiebig II stage, 28 (12.5%) as Fiebig III, 58 (25.9%) as Fiebig IV and 100 (44.6%) as Fiebig V. None was diagnosed at Fiebig I stage. The majority of patients, 141 (63.2%), were Spanish-born, whereas 82 (36.8%) were migrant. The main risk factor for HIV infection acquisition was men-who-have-sex-with-men (MSM), present in 190 (85.6%) patients, followed by heterosexual relations, 21 (9.5%) patients, and intravenous drug users (IVDU), 11 (5.0%) patients. Thirty-six (16.1%) patients presented with concomitant STD (syphilis or/and Hepatitis virus C) and 30 (13.4%) presented other comorbidity (by Charlson index).

Characteristics of severe PHI

Of the 74 (33%) patients presenting a severe PHI, 30 (13.4%) patients qualified as severe PHI according to clinical criteria, three (1.3%) patients presented bacterial pneumonia, 14 (6.3%) oral candidiasis, seven (3.1%) pharyngeal candidiasis, two (0.9%) esophageal herpes, 11 (4.9%) meningoencephalitis, one (0.4%) prolonged fever (over 1 month) and one (0.4%) prolonged diarrhea (over 1 month). With respect to immunological severity criteria, a

Table 1
Epidemiologic and clinical characteristics of patients with PHI and differences between severe and non-severe patients.

Condition	Overall N = 224	Severe N = 74	Non-severe N = 150	p
Fiebig at diagnosis[a]				0.279
II (positive p24)	38 (17.0)	17 (23.0)	21 (14.0)	0.767
III (positive ELISA)	28 (12.5)	10 (13.5)	18 (12.0)	0.747
IV (indeterminate Western blot)	58 (25.9)	15 (20.3)	43 (28.7)	0.177
V (incomplete Western blot)	100 (44.6)	32 (43.2)	68 (45.3)	0.767
Gender				
Male	210 (93.8)	71 (95.9)	139 (92.7)	0.340
Female	14 (6.3)	3 (4.1)	11 (7.3)	
Age at diagnosis[b]	35 ± 8	36 ± 9	34 ± 8	0.142
Origin				
Spain	141 (63.2)	43 (58.1)	98 (65.8)	0.264
Migrant	82 (36.8)	31 (41.9)	51 (34.2)	
HIV risk factor				
HTX	21 (9.5)	6 (8.2)	15 (10.1)	0.616
MSM	190 (85.6)	62 (84.9)	128 (85.9)	
IDU	11 (5.0)	5 (6.8)	6 (4.0)	
Symptomatic PHI	190 (84.8)	73 (98.6)	117 (78.0)	<0.001
Fever	180 (80.4)	71 (95.9)	109 (72.7)	<0.001
Fever ≥7 days	110 (53.9)	55 (77.5)	55 (41.4)	<0.001
Asthenia	139 (62.1)	58 (78.4)	81 (54.0)	<0.001
Rash	80 (35.7)	36 (48.6)	44 (29.3)	0.005
Headache	76 (33.9)	34 (45.9)	42 (28.0)	0.008
Myalgia	101 (45.1)	36 (48.6)	65 (43.3)	0.452
Night sweating	49 (21.9)	18 (24.3)	31 (20.7)	0.533
Pharyngitis	83 (37.1)	34 (45.9)	49 (32.7)	0.053
Oral/genital ulcers	38 (17.0)	16 (21.6)	22 (14.7)	0.192
Splenomegaly	4 (1.8)	3 (4.1)	1 (0.7)	0.072
Hepatomegaly	10 (4.5)	5 (6.8)	5 (3.3)	0.243
Gastrointestinal symptoms	67 (29.9)	32 (43.2)	35 (23.3)	0.002
Lymphadenopathies	98 (43.8)	38 (51.4)	60 (40.0)	0.107
Hospitalization required	57 (25.4)	35 (47.3)	22 (14.7)	<0.001
Concomitant STD	36 (16.1)	6 (8.1)	30 (20.0)	0.023
Comorbidities	30 (13.4)	14 (18.9)	16 (10.7)	0.088
ART scheme				
2NRTI + NNRTI	64 (30.0)	20 (28.6)	44 (30.8)	0.862
2NRTI + InSTI	56 (26.3)	20 (28.6)	36 (25.2)	
2NRTI + PI	93 (43.7)	30 (42.9)	63 (44.1)	
ART beginning <1 month	71 (31.7)	31 (41.9)	40 (26.7)	0.021
ART beginning <3 months	124 (55.4)	41 (55.4)	83 (55.3)	0.992
ART beginning <6 months	147 (65.6)	52 (70.3)	95 (63.3)	0.304

Abbreviations: HTX = heterosexual, MSM = Men Sex Men, IDU = Intravenous Drug Users, ART = Antiretroviral Treatment, NRTI = Nucleoside Reverse Transcriptase Inhibitor, NNRTI = Non Nucleoside Reverse Transcriptase Inhibitor, InSTI = Integrase Strand Transfer Inhibitor, PI = Protease Inhibitor.
[a] N (%).
[b] Mean ± standard deviation.

CD4 count inferior to 350 cells/mm^3 was present in 56 (25%) patients, severe thrombocytopenia was found in five (2.4%) patients and non-viral hepatitis in six (2.9%) patients (Table 2).

Comparison of epidemiological, clinical, immunological and virological features between severe PHI and non-severe PHI

The differences in baseline characteristics between the severe and non-severe groups are represented in Tables 1 and 3. The mean year of infection was 2009 for the severe group and 2008 for the non-severe ($p = 0.148$). Regarding virological features, significant differences were found between both groups in baseline viral load, presenting a mean of 5.71 log10 copies/mL in the severity group and 4.81 log10 copies/mL in the non-severe group ($p < 0.001$). No significant differences were observed in viral tropism or in viral subtype between groups. No significant differences were found in the proportion of primary transmitted drug resistance mutations between groups (9.34% in the non-severe vs. 4.05% in the severe, $p = 0.160$) (Tables 1 and 3).

Table 2
Clinical, biochemical and immunological characteristics of patients with severe PHI (N = 74).

Severe PHI condition	74 (33)[a]
Clinical severity[b]	30 (13.4)
Hepatitis[c,d]	6 (2.9)
Bacterial pneumonia	3 (1.3)
Oral candidiasis	14 (6.3)
Esophageal candidiasis	7 (3.1)
Esophageal herpes[e]	2 (0.9)
Fever > 1 month	1 (0.4)
Diarrhea >1 month	1 (0.4)
Meningoencephalitis[f]	11 (4.9)
CD4 at diagnosis below 350 cells/mm^3	56 (25.0)
Platelets at diagnosis below 100[c]	5 (2.4)

Abbreviations: PHI = Primary HIV Infection.
[a] N (%).
[b] Any of the below criteria.
[c] Platelets n = 206, transaminases n = 208.
[d] Active HBV/HCV infection excluded.
[e] In 2 cases, together with esophageal candidiasis.
[f] In 2 cases, together with oral candidiasis.

Table 3
Main coagulation, biochemical, immunological and virological features of patients with PHI and differences between severe and non-severe patients (N = 224).

Parameter	N	Overall N = 224	Severe N = 74	Non-severe N = 150	p
Coagulation variables					
Platelets[a] ($\times 10^9$/L)	206	241.25 ± 87.86	217.90 ± 98.94	254.06 ± 78.62	0.004
Biochemical variables					
Creatine Kinase (IU/L)	176	145.69 ± 209.02	141.08 ± 184.96	148.13 ± 221.46	0.832
ASAT (mU/mL)	208	56.00 ± 93.87	87.42 ± 132.59	39.01 ± 57.76	<0.001
ALAT (mU/mL)	208	78.07 ± 127.18	120.85 ± 161.66	54.94 ± 97.00	<0.001
GGT (IU/L)	200	58.89 ± 89.30	91.89 ± 125.54	40.34 ± 52.16	<0.001
AP (IU/L)	199	171.28 ± 172.52	203.90 ± 271.02	152.79 ± 66.53	0.044
Bilirubin (mg/100 mL)	205	0.60 ± 0.29	0.57 ± 0.24	0.61 ± 0.32	0.301
LDH (IU/mL)	190	479.62 ± 208.21	564.93 ± 294.46	432.07 ± 115.48	<0.001
Immunological variables					
CD4 (cells/mm^3)	224	523.21 ± 280.70	322.69 ± 142.16	622.13 ± 285.63	<0.001
CD8 (cells/mm^3)	222	1.134.13 ± 822.96	1.093.37 ± 1073.63	1.154.09 ± 670.32	0.607
CD4/CD8	222	0.65 ± 0.49	0.53 ± 0.52	0.71 ± 0.46	0.009
Virological variables					
Viral load ($\log_{10}$ copies/mL)	218	5.11 ± 1.18	5.71 ± 0.93	4.81 ± 1.18	<0.001
Viral subtype[b]	139				0.799
B subtype		114 (82)	38 (80.9)	76 (82.6)	
Non-B subtype		25 (18)	9 (19.1)	16 (17.4)	
TDR[b]					
Overall		17 (7.59)	3 (4.05)	14 (9.34)	0.160
PI[1]		3 (1.34)	0	3 (2.0)	0.220
NRTI[2]		3 (1.34)	0	3 (2.0)	0.220
NNRTI[3]		11 (4.91)	3 (4.05)	8 (5.34)	0.676
Tropism[b]	90				0.172
R5		72 (80.0)	26 (83.9)	46 (78.0)	
X4		12 (13.3)	5 (16.1)	7 (11.9)	
Dual		6 (6.7)	0 (0.0)	6 (10.2)	

Abbreviations: ASAT (aspartate aminotransferase), ALAT (alanine aminotransferase), GGT (gamma-glutamyl transpeptidase), AP (alkaline phosphatase), LDH (lactate dehydrogenase).
[a] Mean ± standard deviation.
[b] Frequency (%).
[1] Patients with at least one TDR for PI, including: M46I/L, V82T/F/A, L90M, Q58E, I84V, I54L.
[2] Patients with at least one TDR for NRTI, including: T215F/Y/X, M41L, L210W, K219E/Q, K219R, K70R, D67N, K219E/Q, K219N/R, M184V, T69N.
[3] Patients with at least one TDR for NNRTI, including: Y181C, V108I, K103N, K101E, E138A.

From the clinical standpoint, significant differences were observed in the proportion of patients presenting fever (95.9% in severe PHI vs 72.7% in non-severe PHI; p < 0.001), patients with fever duration longer than one week (77.5% vs 41.4%; p < 0.001), asthenia (78.4% vs 54%; p < 0.001), skin rash (48.6% vs 29.3%; p = 0.005), headache (45.9% vs 28%; p = 0.008), mononucleosis-like syndrome (20.3% vs 9.3%; p = 0.022) and gastrointestinal symptoms (43.2% vs 23.3%; p = 0.002). However, no significant differences were observed among the proportions of patients presenting myalgia, nocturnal sweating, pharyngitis, ulcers, splenomegaly, hepatomegaly, and lymphadenopathies.

Finally, in the epidemiological data, patients with severe PHI presented significantly less concomitant STDs than non-severe patients (8.1% vs 20%; p = 0.023). Also, the proportion of patients requiring hospitalization during the PHI was significantly higher in the severe group (47.3% vs 14.7%, p < 0.001). No significant differences were found in Fiebig stage at diagnosis, gender, age at diagnosis, origin, HIV risk factor and Charlson index (Table 1).

Virological and immunological response to early ART beginning

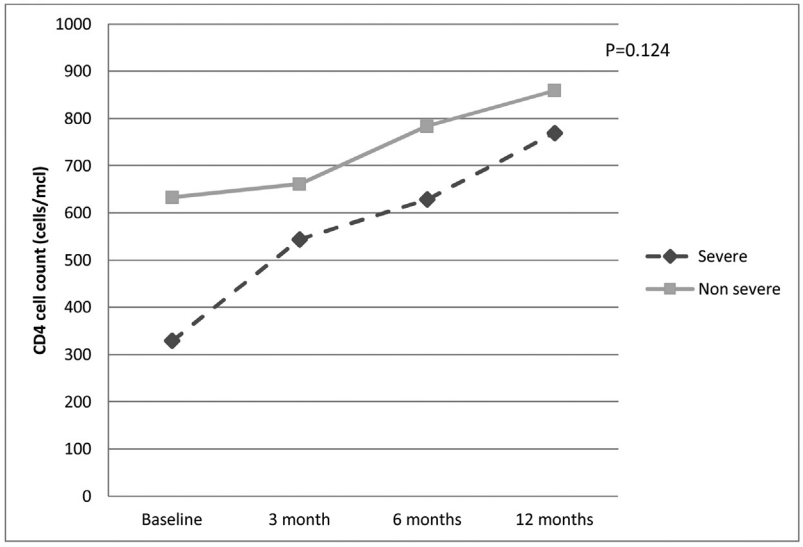
For the analysis of the virological and immunological outcome, we included every patient starting ART during the first six months of infection (n = 147) and follow up for one year from starting ART. A progressive increase in CD4 cell counts was observed at three, six and 12 months in both severe and non-severe PHI groups: 544.38 cells/mm^3, 628.8 cells/mm^3 and 769.85 cells/mm^3 respectively in the severe group (329.67 cells/mm^3 at baseline) and 661.48 cells/mm^3, 784.06 cells/mm^3, 859.19 cells/mm^3 in the non-severe group (633.16 cells/mm^3 at baseline). These differences were statistically significant at six months (p = 0.003), being comparable at 12 months (p = 0.124) (Figure 2a). No significant variations were detected in the CD8 cell count. CD4/CD8 ratio presented a significant trend, increasing progressively at three, six and 12 months: 0.59, 0.75 and 0.93 respectively (0.51 at baseline) in the severe group and 0.81, 0.99, 1.14 (0.69 at baseline) in the non-severe group (p = 0.014 at month 12). Finally, viral load suppression is shown in Figure 2b. The proportion of patients with undetectable viral load increases progressively from baseline to three, six and 12 months; being 2.9%, 64% and 93.8% respectively in the severe group and 11.5%, 73.9% and 95.2% in the non-severe group, with no significant differences at any time point. We also analyzed the immunological and virological responses to ART in three time periods (1997-2003, 2003-2008, 2009-2015) in order to identify differences in the outcome due to management recommendations for PHI or different ART schemes, without finding statistically significant differences (see Supplementary material).

As shown in Table 1, no significant differences were found in the proportion of patients beginning ART in the first three to six months after HIV diagnosis. However, the proportion of patients starting ART during the first month was significantly higher in the severe group (41.9% vs 26.7%, p = 0.021). No differences were found in either group regarding the ART treatment scheme.

Clinical outcome

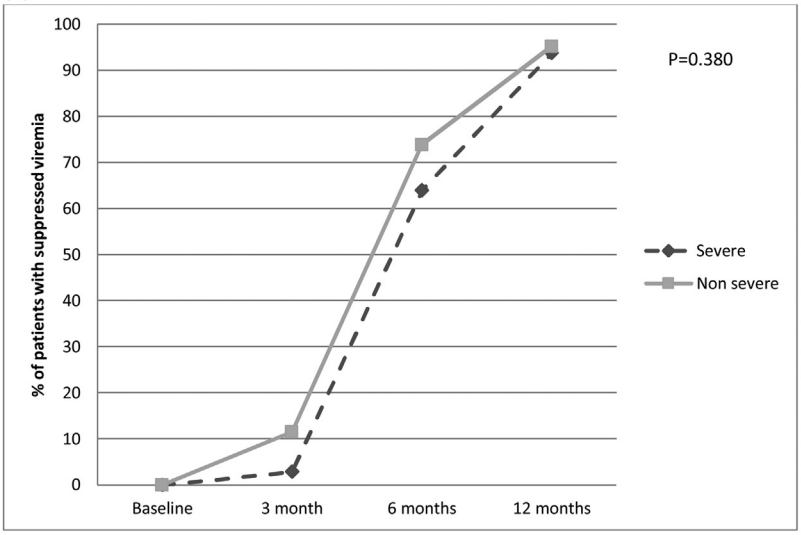
No patient died during the PHI phase. Only three (1.7%) patients out of 224 died during the follow up, two from the non-severe group (1 drug overdose after 6.2 years of follow up and 1 pulmonary Kaposi sarcoma due to a limited adherence to ART after 2.1 years of follow up) and one from the severe group (unknown cause of death occurring after 7.9 years of follow up).

(a)



Patients at risk (n)	Baseline	3 months	6 months	12 months
Severe	52	37	50	48
Non-severe	95	54	91	87

(b)



Patients at risk (n)	Baseline	3 months	6 months	12 months
Severe	52	39	49	50
Non-severe	95	54	92	92

Figure 2. (a) Evolution of CD4 cells at 12 months in patients starting antiretroviral treatment within the first 180 days of PHI diagnosis (N = 147). (b) Evolution of viral load suppression at 12 months in patients starting antiretroviral treatment within the first 180 days of PHI diagnosis.

Discussion

Of the 224 patients presenting with PHI (Fiebig stages I-V) at the Hospital Clinic of Barcelona, 33% presented a severe infection according to our study definition, with clinical severity present in 13%, immunological severity (CD4 count <350 cells/mm^3) in 25% and neurological events in 4.9%. These results are consistent with previous reports from the CASCADE cohort (Lodi et al., 2013), although in this cohort only 14.9% of patients presented clinical severity. The criteria for severity were similar in both cohorts: 28.3% presented CD4 counts below 350 cells/mm^3 and neurologic involvement was present in 4.5%. The cohorts differ in several

epidemiological characteristics: in the present cohort, 85.6% of patients were MSM as an HIV risk factor, whereas in the Lodi S et al study it is 71%. There are also differences in gender (6.3% vs 15% female) and median age at diagnosis (35 vs 29 years). However, both cohorts were comparable in terms of median CD4 counts at diagnosis.

Only a few published studies have compared clinical, immunological, analytical and virological characteristics between severe and non-severe PHI. However the correlation between viral load at PHI, viral load set point and symptoms is well established in English-language literature (Kelley et al., 2007; Robb et al., 2016). According to our data, severe PHI was associated with a significantly higher viral load at diagnosis, resulting in a one logarithmic difference (5.71 log10 vs 4.81 log10 copies/mL). These results are consistent with those described by Braun et al, who established a correlation between severity (which they had previously defined on the basis of neurological symptoms, hospitalization, age, elevated fever, elevated liver enzymes and thrombocytopenia, and viral load and CD4 cell count at baseline) and higher viral load and lower CD4 cell counts (Braun et al., 2014). It is well known that X4 viral tropism is associated with lower baseline CD4 cell count, higher viral load and major risk of disease progression (Daar et al., 2007), but no relationship was discovered between viral tropism and PHI severity in our study, although the small proportion of X4 patients in our cohort limits the statistical power of this association.

In the epidemiological data, no significant differences were found between groups in Fiebig stage, gender, age at diagnosis, associated comorbidities or risk factor for HIV infection, which suggests that the severity of the PHI does not depend on the route of transmission. Surprisingly, significant differences were observed when comparing groups for the presence of concomitant STDs at diagnosis, where non-severe forms appeared to be more associated to a higher prevalence of STDs (8.1% in severe PHI vs 20.0% in non-severe PHI). This association may be explained by a more frequent and earlier consultation in hospitals of patients with STDs, causing a more frequent and earlier HIV diagnosis rate, even in asymptomatic patients.

The CD4 T-cell count differences between groups are not comparable because low CD4 count at diagnosis was one of the defining criteria for severity. However, it is interesting to highlight that no significant differences were seen in CD8 cell counts, which in both groups greatly increased, showing that, when faced with a PHI, high immune system activation is present independent of the presence or otherwise of a severe form.

This study compared the response to early ART (i.e., administrated in a period of time below 180 days from the diagnosis) from severe and non-severe PHI and showed that, despite the one log10 copies/mL difference in viral load between both groups at baseline, there is a trend to suppression until being undetectable in proportions over 90% in both groups in the period of a year. Furthermore, the proportion of viral suppression after ART initiation did not show any significant difference at any time point. Remarkably, early ART initiation was also associated with a progressive increase in CD4 cell counts in both groups (increasing in 471.79 cells/mm^3 in the severe group and 239.85 cells/mm^3 in the non-severe group) being comparable at 12 months from the diagnosis. However, patients with non-severe PHI presented a significantly higher CD4/CD8 ratio at 12 months (0.93 vs 1.14 $p = 0.014$), consistent with the results of Hoenigl et al, who found an association between symptomatic acute HIV infection and a lower CD4/CD8 ratio (Hoenigl et al., 2016). The association between lower CD4/CD8 ratio and non-AIDS mortality has been well described (Serrano-Villar et al., 2014; Mussini et al., 2015), justifying further long-term studies to evaluate the impact of severe PHI in non-AIDS mortality.

When comparing the severity of PHI and the time to starting ART, no differences were found in the proportion of patients starting ART within the first two, three and six months; however, more patients with severe PHI started ART in the first month than did patients with non-severe PHI. This fact confirms that patients presenting severity criteria tend to begin ART more quickly. It is worth noting that in contrast to other countries (Mehraj et al., 2018), the Spanish health system is free for all people living in Spain, so there is no economic bias expected in time to ART initiation in this context. Finally, although a low mortality rate is expected for this condition, it is important to highlight that, although the sample is very small, severity of PHI does not seem to imply a worse outcome in terms of survival rate. There were no deceases during the initial phase of HIV infection (first 12 months).

Conclusions

Up to 33% of patients from our PHI cohort presented a severe PHI. Viral load was significantly higher in severe forms, which were also more symptomatic as expected by definition, required more hospital admissions, and presented a higher proportion of abnormal analytical parameters, such as liver function tests. However, when ART is started early, the immunological or virological outcomes at 12 months were comparable between patients with and without severe PHI, although non-severe patients have a significantly higher CD4/CD8 ratio.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

This work was conceived by JMM, DN and AS. Data was collected and managed by EF, CL, DN and AS. Statistical analysis was performed by DN, AS, with the supervision of JMM, JA, CM. DN wrote the manuscript with the input of all of the authors. All authors contributed in producing the article, by drafting the work or revising it critically. All authors have had access to the final version and have approved it to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were properly investigated and resolved.

Ethical issues

All patients signed were required to give written consent at the inclusion in the cohort. PHI-HCB Cohort had been previously approved by the Hospital Clínic Institutional Review Board.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.08.001.

References

Ambrosioni J, Artigues F, Nicolás D, Peñafiel J, Agüero F, Manzardo C, et al. Neurological involvement in patients with acute/recent HIV-1 infection. A case-control study. J Neurovirol 2017;23(October 5):679–85.

Braun DL, Kouyos R, Oberle C, Grube C, Joos B, Fellay J, et al. A novel acute retroviral syndrome severity score predicts the key surrogate markers for HIV-1 disease progression. López-Galíndez C, editor. PLoS One 2014;9(December 12)e114111.

Braun DL, Kouyos RD, Balmer B, Grube C, Weber R, Günthard HF. Frequency and spectrum of unexpected clinical manifestations of primary HIV-1 infection. Clin Infect Dis 2015;61(6):1013–21.

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83.

Daar ES, Kesler KL, Petropoulos CJ, Huang W, Bates M, Lail AE, et al. Baseline HIV type 1 coreceptor tropism predicts disease progression. Clin Infect Dis 2007;45 (September 5):643–9.

European AIDS Clinical Society. European AIDS Clinical Society (EACS) Guidelines. Version 9. 2017.

Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 2003;17 (September 13):1871–9.

Günthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults. JAMA 2016;316 (July 2):191.

Hoenigl M, Chaillon A, Little SJ. CD4/CD8 T cell ratio in acute HIV infection and the impact of early antiretroviral therapy. Clin Infect Dis 2016;63(3): 425–6.

INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med 2015;373(August 9):795–807.

Kelley CF, Barbour JD, Hecht FM. The relation between symptoms, viral load, and viral load set point in primary HIV infection. J Acquir Immune Defic Syndr 2007;45(August 4):445–8.

Lodi S, Fisher M, Phillips A, De Luca A, Ghosn J, Malyuta R, et al. Symptomatic illness and low CD4 cell count at HIV seroconversion as markers of severe primary HIV infection. Speck RF, editor. PLoS One 2013;8(November 11):2–9.

Mehraj V, Cox J, Lebouché B, Costiniuk C, Cao W, Li T, et al. Socio-economic status and time trends associated with early ART initiation following primary HIV infection in Montreal, Canada: 1996 to 2015: 1996. J Int AIDS Soc 2018;21 (February 2), doi:http://dx.doi.org/10.1002/jia2.25034.

Mussini C, Lorenzini P, Cozzi-Lepri A, Lapadula G, Marchetti G, Nicastri E, et al. CD4/CD8 ratio normalisation and non-AIDS-related events in individuals with HIV who achieve viral load suppression with antiretroviral therapy: an observational cohort study. Lancet HIV 2015;2(March 3):e98–106.

Nicolás D, Ambrosioni J, de Lazzari E, Suarez A, Manzardo C, Agüero F, et al. Epidemiological changes of acute/recent human immunodeficiency virus type 1 infection in Barcelona, Spain (1997–2015): a prospective cohort study. Clin Microbiol Infect 2018;25(7):878–84.

Robb ML, Eller LA, Kibuuka H, Rono K, Maganga L, Nitayaphan S, et al. Prospective Study of Acute HIV-1 Infection in Adults in East Africa and Thailand. N Engl J Med 2016;374(22):2120–30.

Schneider E, Whitmore S, Glynn KM, Dominguez K, Mitsch A, McKenna MT, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged. MMWR Recomm Reports Morb Mortal Wkly Report Recomm Reports 2008;57(December RR-10):1–12.

Serrano-Villar S, Sainz T, Lee SA, Hunt PW, Sinclair E, Shacklett BL, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. Silvestri G, editor. PLoS Pathog 2014;10(May 5)e1004078.

Sued O, Miró JM, Alquezar A, Claramonte X, García F, Plana M, et al. Primary human immunodeficiency virus type 1 infection: clinical, virological and immunological characteristics of 75 patients (1997-2003). Enferm Infecc Microbiol Clin 2006;24(4):238–44.