Case Report: Rapid HIV Progression During Acute HIV-1 Subtype C Infection in a Mozambican Patient with Atypical Seroconversion

Cesar Velasco, Erica Parker, Lucia Pastor, Abel Nhama, Salesio Macuacua, Inácio Mandomando, Julià Blanco,[†] and Denise Naniche^{*†}

ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain; Department of Preventive Medicine and Epidemiology, Hospital Clinic, Barcelona, Spain; School of Paediatrics and Child Health, University of Western Australia, Perth, Australia; IrsiCaixa Institute for AIDS Research, Institut Germans Trias i Pujol (IGTP), Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, UAB, Badalona, Spain; Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique; Instituto Nacional de Saúde, Ministério de Saúde, Maputo, Mozambique; Universitat de Vic- Universitat Central de Catalunya, Vic, Spain

Abstract. Acute human immunodeficiency virus (HIV) infection (AHI) refers to the period between viral transmission and development of an adaptive immune response to HIV antigens (seroconversion) usually lasting 6–8 weeks. Rare cases have been described in which HIV-infected patients fail to seroconvert and instead, develop rapid HIV-mediated clinical decline. We report the case of a Mozambican woman with AHI and malaria coinfection who showed atypical seroconversion and experienced rapid deterioration and death within 14 weeks of diagnosis with AHI. Atypical seroconversion may be associated with rapid progression. Fourth generation rapid tests could lead to earlier identification and intervention for this vulnerable subgroup.

INTRODUCTION

Acute human immunodeficiency virus (HIV) infection (AHI) refers to the period between viral infection and the development of an adaptive immune response to HIV antigens (seroconversion) usually lasting 6–8 weeks.^{1,2} This period is typically associated with high viral loads, a massive early innate immune response, and a rapid decrease in CD4⁺ T-lymphocyte counts. In parallel, an HIV-specific humoral immune response is mounted, leading to seroconversion.^{3,4} Rare cases have been described in which HIV-infected patients do not develop the classic antiviral antibody response and instead, develop a fast HIV-mediated immunodepression and rapid clinical progression.^{5–7} We report the case of a 30-year-old black Mozambican woman with acute HIV infection and *Plasmodium falciparum* malaria coinfection who showed an atypical pattern of seroconversion and experienced rapid deterioration and death within 14 weeks of diagnosis with AHI.

CASE REPORT

The patient presented to the Manhiça District Hospital in Mozambique with a febrile syndrome, was referred, and gave informed consent to an ongoing study of acute HIV. The patient had no prior history of HIV testing and tested negative for an HIV antibody rapid test (Determine HIV 1/2; Abbott Laboratories, Chicago, IL), but plasma reverse transcription polymerase chain reaction (real-time-PCR) revealed a high HIV viral load (log₁₀ 6.7 copies/mL) (all results are in Table 1), thus identifying a case of AHI. Both malaria slide and sputum smear for tuberculosis (TB) at this time were negative.

Subsequently, the patient was seen three times in 14 weeks of follow-up. HIV rapid testing on two occasions revealed indeterminate HIV serology (positive for Determine but neg-

ative for Unigold; Trinity Biotech Co., Wicklow, Ireland) (Table 1). At the 1-month follow-up visit (day 34), the patient had complaints of paroxysmal diarrhea, fever, night sweats, and productive cough with mucoid expectoration. Sputum samples continued to be negative for TB, and no pathological signs were observed on chest X-ray. Her hematology was normal; however, her CD4 counts were 64 cells/mm³ (Table 1). She was diagnosed with *P. falciparum* malaria by blood film (Table 1) and treated with first-line antimalarial treatment (artemether and lumefantrine). At her 2-month follow-up visit (day 64), the patient reported migraine, dizziness, cough, and continued weight loss. She was prescribed metronidazole for treatment of *Clostridium difficile*, and cotrimoxazole prophylaxis was initiated. Her CD4 counts had fallen to 33 cells/mm³, and HIV RNA levels remained above 6.0 log₁₀ copies/mL (Table 1). Quantitative PCR for *P. falciparum* revealed low parasitemia (69 parasites/μL). Although antiretroviral treatment (ART) in the absence of confirmed seroconversion is not included in the Mozambican national guidelines, the patient was referred to start outpatient counseling for ART.

Five days later, the patient's condition had further deteriorated. She had notably rapid weight loss, and clinicians were suspicious of acquired immune deficiency syndrome (AIDS) wasting syndrome. Clinicians agreed that TB treatment followed by ART should be initiated according to national guidelines. During the next few weeks, the patient declined follow-up by field workers and did not return to the clinic. An additional field worker home visit reported that the patient died at home 14 weeks post-diagnosis.

Sequencing RT and Protease from plasma samples from three visits (days 0, 34, and 64) confirmed infection by HIV-1 subtype C and C-C chemokine receptor type 5 (CCR5) tropism. Furthermore, sequencing of the gp120 V3 region in all samples showed identical sequences over the 2-month period. P24 antigen was detected in plasma at 1 month by enzyme-linked immunosorbent assay (ELISA). Western blot (WB) analysis showed an atypical profile across time points with antibody positivity against gp41, gp120, and p31, while remaining negative for p24 and p17 gag-specific antibodies (Table 1). The pattern was atypical, because there was no detectable

^{*} Address correspondence to Denise Naniche, ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Rosselló 132, 08036 Barcelona, Spain. E-mail: dsuzanne@clinic.ub.es

[†] These authors contributed equally.

TABLE 1
Patient results at initial and follow-up visits

	Visit 1 (day 0)	Visit 2 (day 34)	Visit 3 (day 64)
HIV viral load (log ₁₀ copies/mL)	Log ₁₀ 6.7	Log ₁₀ 6.3	Log ₁₀ 6.4
Determine HIV-1/2 rapid test	–	+	+
UniGold rapid test	ND	–	–
WB	gp41++	gp41++	gp41++
WB	gp120+/-	gp120+/-	gp120+
WB	p31+/++	p31+/++	p31+
WB	p24–	p24–	p24–
WB	p17–	p17–	p17–
p24 ELISA (pg/mL)	388	ND	ND
Lymphocytes (cells/μL)	ND	1,656	998
T cells (cells/μL)	ND	963	566
T cells (% of lymph)	ND	58	57
CD4 T-cell counts (cells/μL)	ND	64	33
CD4 T cell (% of lymph)	ND	4	3
CD8 T-cell counts (cells/μL)	ND	742	460
CD8 T cell (% of lymph)	ND	45	46
Ratio CD4/CD8	ND	0.09	0.07
Red blood cells (10 ⁶ cells/μL)	ND	4.19	ND
Hemoglobin (g/dL)	ND	11.0	ND
Hematocrit (%)	ND	33.1	ND
MCV (fL)	ND	79.0	ND
White blood cells (10 ³ cells/μL)	ND	4.20	ND
Neutrophils (10 ³ cells/μL)	ND	2.09	ND
Lymphocytes (10 ³ cells/μL)	ND	1.57	ND
Monocytes (10 ³ cells/μL)	ND	0.46	ND
Eosinophils (10 ³ cells/μL)	ND	0.04	ND
Platelets (10 ³ cells/μL)	ND	191	ND
Malaria blood film*	–	3,240	ND
Syphilis	ND	–	ND
TB	–	–	ND
Hepatitis B	ND	–	ND

ND = not done.

*Blood film microscopy expressed in parasites per microliter.

antibody to gag proteins. Recognition of gp120 increased over time, reflecting a slow seroconversion process. Human Leukocyte Antigen (HLA) System typing showed homozygosity at all loci, except for HLA-A (HLA-A*02, A*26, B*58, –; C*07, –; DRB1*11, –; DQB1*03, –).

DISCUSSION

A substantial subset of HIV-1-infected individuals experience a sharp decline in CD4 T-cell counts quickly after primary infection, with progression to AIDS occurring within the first 1–3 years of infection.⁸ These rapid progressors are estimated to comprise 10–15% of HIV-1 cases,⁸ although exact figures are unknown, particularly in resource-poor settings. HLA homozygosity as well as certain HLA types are associated with rapid HIV progression.^{9–11} Seronegative HIV infection is also described to be associated with high viral loads, rapid disease progression, and significant mortality.¹² Seronegative HIV infections are rare and have been hypothesized to occur by overwhelming a particularly susceptible host immune system with HIV antigen.¹³ The clinical presentations of two known case reports of seronegative subtype C infection are very similar to that observed in our patient.^{14,15}

In the Mozambican patient, seroconversion was slow in the presence of rapid disease progression. This patient was rapid test indeterminate on two occasions and showed increasingly positive WB results, suggesting that she developed an initial humoral response but that the response never fully matured.

Furthermore, the patient's lack of gp120 V3 region sequence diversity was consistent with a poor antibody response, resulting in little immune selection pressure. Although the lack of anti-gag antibodies has been also reported in late-stage AIDS,^{16,17} the shift from negative to positive Determine rapid test over time, the high viral load at diagnosis, which subsequently declined, the uniformity of the gp120 V3 region, and the HLA pre-disposition argue for severe primary infection.

The combination of coinfection with *P. falciparum* malaria and extreme homozygosity for all HLA loci may have contributed to this patient's atypical seroconversion and rapid HIV progression. The patient was diagnosed with *P. falciparum* malaria at day 34 by microscopy, but we cannot exclude that she had submicroscopic *P. falciparum* infection at her initial day 0 visit. She still had low parasitemia at day 64, despite antimalarial treatment. *P. falciparum* has been shown to lead to immune activation, increased HIV replication, and a decrease in CD4 counts during chronic HIV infection.^{18–20} However, there is no information on *P. falciparum* infection during acute HIV infection. The heightened state of immune activation associated with *P. falciparum* coinfection may have led to early HIV-specific clonal depletion of CD4 T cells, resulting in impairment of both B- and T-cell responses as described for acute HIV infection in a psoriasis patient.¹³ In addition, the extreme homozygosity of this patient may have led to a narrow or insufficient HIV-specific CD8 T-cell response, thus allowing for heightened HIV replication. Although the patient was negative for TB, we cannot exclude atypical TB presentations, which have been observed for HIV patients.^{21,22} In Mozambique, as in much of sub-Saharan Africa, routine HIV diagnoses are based on rapid antibody testing algorithms, and HIV RNA detection is not readily available. Consequently, there are no provisions in national treatment guidelines for patients who have negative or indeterminate rapid HIV test results but progress to AIDS. Outside of the context of a specific study, it is unlikely that this patient would have been identified as HIV-positive, much less as rapidly progressing.

The frequency of inadequate serological immune responses to HIV subtype C infections resulting in poor outcomes is unknown and not likely to be high. It may be plausible to speculate that, in areas of high HIV incidence, widespread coinfection with malaria (and indeed, other organisms) could impair or skew antibody responses and more commonly, lead to rapidly progressing HIV infection in the absence of an HIV diagnosis. HLA combinations pre-disposing to rapid progression could contribute to undermining the HIV-specific immune response during acute HIV complicated by malaria. Under existing antibody-reliant diagnostic algorithms, these HIV infections would go unidentified. This might warrant the use of HIV diagnostic tests that are able to detect HIV at an earlier stage. Fourth generation rapid diagnostic tests including detection of p24 are becoming available, and their use could aid in the identification of HIV rapid test-negative or indeterminate acute infections in resource-poor settings and lead to earlier intervention for this vulnerable subgroup with high mortality rates.

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Authors' addresses: Cesar Velasco, ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain and Department of Preventive Medicine and Epidemiology, Hospital Clinic, Barcelona, Spain, E-mail: velascomunoz@gmail.com. Erica Parker, School of Paediatrics and Child Health, University of Western Australia, Perth, Australia, E-mail: ericaparker01@gmail.com. Lucia Pastor, ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain; IrsiCaixa Institute for AIDS Research, Institut Germans Trias i Pujol (IGTP), Hospital Germans Trias i Pujol, UAB, Badalona, Spain, and Centro de Investigaçao em Saúde de Manhica (CISM), Maputo, Mozambique, E-mail: Lucia.Pastor@manhica.net. Abel Nhama and Inácio Mandomando, Centro de Investigaçao em Saúde de Manhica (CISM), Maputo, Mozambique, and Instituto Nacional de Saúde, Ministério de Saúde, Maputo, Mozambique, E-mails: Abel.Nhama@manhica.net and inacio.mandomando@manhica.net. Salesio Macuacua, Centro de Investigaçao em Saúde de Manhica (CISM), Maputo, Mozambique, E-mail: Salesio.Macuacua@manhica.net. Julià Blanco, IrsiCaixa Institute for AIDS Research, Institut Germans Trias i Pujol (IGTP), Hospital Germans Trias i Pujol, UAB, Badalona, Spain, and Universitat de Vic, UVIC-UCC, Vic, Spain, E-mail: JBlanco@irsicaixa.es. Denise Naniche, ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, E-mail: dsuzanne@clinic.ub.es.

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