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Acute Human Immunodeficiency Virus (HIV) Syndrome After Nonadherence to Antiretroviral Therapy in a Patient With Chronic HIV Infection: A Case Report

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We report a rare case of acute human immunodeficiency virus (HIV) syndrome in a patient with chronic HIV infection with acute illness indistinguishable from acute retroviral syndrome. The patient presented with an acute febrile mononucleosis-like illness after increasing nonadherence to antiretroviral therapy. A marked increase in HIV RNA level of 1 220 000 copies/mL from less than 20 copies/mL occurred within 3 weeks. The diagnosis of acute HIV syndrome was made after alternative causes of illness were ruled out.

Keywords. acute HIV syndrome; acute retroviral rebound syndrome; chronic HIV infection; nonadherence; viral rebound.

Primary human immunodeficiency virus (HIV) infection is often manifested by acute retroviral syndrome (aka acute seroconversion syndrome or acute HIV infection), which is a mononucleosis-like illness characterized by fever, adenopathy, malaise, nonexudative pharyngitis, myalgia, erythematous rash, headache, nausea, thrombocytopenia, and leukopenia with high plasma HIV RNA level, often exceeding 1 000 000 copies/mL in patients newly infected with HIV. The term "acute HIV syndrome" or "acute retroviral rebound syndrome" has been used in the literature to describe rare cases of recurrent acute illness in patients with chronic HIV infection indistinguishable from acute retroviral syndrome [1–3].

We report a case of acute HIV syndrome that occurred in a patient with chronic HIV infection after patient became nonadherent to antiretroviral therapy (ART).

CASE REPORT

A 49-year-old African-American female was admitted for acute onset of fever for 4 days duration. The patient was diagnosed with HIV type-1 20 years ago and had been on ART for 16 years with stable immunologic and virologic control for years, despite a fairly unconventional ART regimen of lamivudine 150 mg/zidovudine 300 mg (Combivir) and nevirapine 200 mg, both taken once daily instead of twice daily as typically recommended. Due to frequent travel related to her occupation, the patient disclosed increasing nonadherence to ART in the few months before admission, estimating that she took ART 75% of the time 2 months prior and 50% of the time 1 month before admission. Despite her nonadherence, HIV viral load (plasma viral load [pVL]) still had remained undetectable 3 weeks before admission, at which time CD4 count was 853 cells/mm^3.

On admission, fever of 103.4F° was accompanied by malaise, headache, severe myalgia, nausea, and abdominal pain. The patient's history was remarkable for a sick contact with her 1-year-old granddaughter who lives with her. Both had mild flu-like symptoms 3 weeks prior with subjective fever. At that time, the patient had visited her physician at the clinic with unremarkable physical examination and symptoms that lasted 1–2 days with full recovery without any antibiotic treatment. She had not been sexually active and denied any recreational drug use. The patient also had visited Southern Africa 6 months before admission. She received pretravel vaccination for yellow fever and typhoid. Malaria prophylaxis was given, but she did not complete the full course after returning. She denied any other recent vaccinations.

Physical exam was unremarkable except for a 2 × 2 mm healed ulcer in the perirectal area. Laboratory studies before admission, on admission, and after discharge are shown in Table 1. In addition to CD4 and pVL, routine laboratory tests drawn 3 weeks prior to admission were normal. She denied any new medications other than acyclovir, which she started to take again 3 weeks ago for her recurrent genital herpes. Her ART was continued following admission.

Serum polymerase chain reaction (PCR) for *Parvovirus B19*, *Enterovirus*, cytomegalovirus, Epstein-Barr virus, multiplex PCR-based respiratory virus panel, serologic tests for *Histoplasma*

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Table 1. Laboratory Data

Variable	Reference Range	3 Weeks Before Admission, Outpatient Clinic (5/13)	On Admission (6/2)	9 Days After Admission, Outpatient Clinic (6/11)	6 Weeks After Admission, Outpatient Clinic (7/15)
Hematocrit (%)	41.0–53.0	37.4	32.4	33.7	
Hemoglobin (g/dL)	13.5–17.5	12.5	10.9	11.0	
White cell count (per mm^3)	4500–11 000	6400	1500	9600	
Differential count (%)					
Neutrophils	40–70		55	33	
Band forms	0–10		25	2	
Lymphocytes	22–44		11	51	
Atypical lymphocytes	0		2	1	
Monocytes	4–11		4	7	
Eosinophils	0–8		0	2	
Basophils	0–3		1	0	
ANC (per mm^3)			1200		
Platelet count (per mm^3)	150 000–400 000	311 000	73 000	437 000	
Haptoglobin (mg/dL)	36–195		65		
Sodium (mmol/L)	135–145		134		
Potassium (mmol/L)	3.4–4.8		3.9		
Chloride (mmol/L)	100–108		103		
Carbon dioxide (mmol/L)	23.0–31.9		24		
Alkaline phosphatase (U/L)	45–115	95	203 → 287 → 291	221	89
Aspartate aminotransferase (U/L)	10–40	13	123 → 229 → 181	32	19
Alanine aminotransferase (U/L)	10–55	9	76 → 126 →112	41	17
Total bilirubin (mg/dL)	0.1–1.2		0.6		
Indirect bilirubin			0.2		
Creatinine Kinase (U/L)	0–145		627 → 1609		
CD4 (per mm^3)	511–2245	853	147	767	
Viral load (copies/mL)	ND	ND	1 220 000		ND

Abbreviations: ANC, absolute neutrophil count; ND, not detectable.

and *Coccidioidomycosis*, and serum *Cryptococcus* antigen were all negative. Viral hepatitis panel, including hepatitis A, B, and C, was negative. In addition to serologic studies, blood smear for malaria, stool culture for *Salmonella*, and blood cultures for bacteria, including mycobacteria and fungi, were all negative.

On hospital day 3, patient defervesced with improving symptoms and pancytopenia, and she started to recover gradually while her ART was resumed on standard dose on admission. Meanwhile, her pVL returned markedly elevated at 1 220 000 copies/mL (6.09 $\log_{10}$). The diagnosis of acute retroviral syndrome secondary to high HIV viremia was made, and ART was switched to tenofovir (TDF), emtricitabine (FTC), and dolutegravir on hospital day 4 after HIV genotyping was sent out. Within 2 weeks after resuming ART, her symptoms resolved completely.

DISCUSSION

Our case describes profound viral rebound observed in a patient chronically infected with HIV resulting in acute severe illness (ie, acute HIV syndrome). Few cases have been reported with an acute illness that resembled acute retroviral syndrome after discontinuation of suppressive ART along with dramatic increase in pVL [1–3]. The marked level of viremia that occurred in relatively short period (3 weeks) in our patient may be explained by the high number of CD4 target cells available, contributing to higher viral burden. This result is supported by previously reported cases with relatively high CD4 cell counts noted before the onset of symptoms [1–3]. We also speculate that her suboptimal regimen may have also contributed by not optimally decreasing the viral reservoir size while on treatment. Previous studies suggest that, after protocol-indicated cessation of ART, patients chronically infected with HIV rebound more rapidly with pVL than patients with primary HIV infection [4]. In the AIDS Clinical Trials Group 5170 study, which evaluated the safety of treatment interruption (TI) in 167 patients, only 1 case of acute retroviral rebound syndrome (0.6%) was documented, but 26 patients (16%) reported Grade 3 or 4 signs and symptoms with musculoskeletal pain,

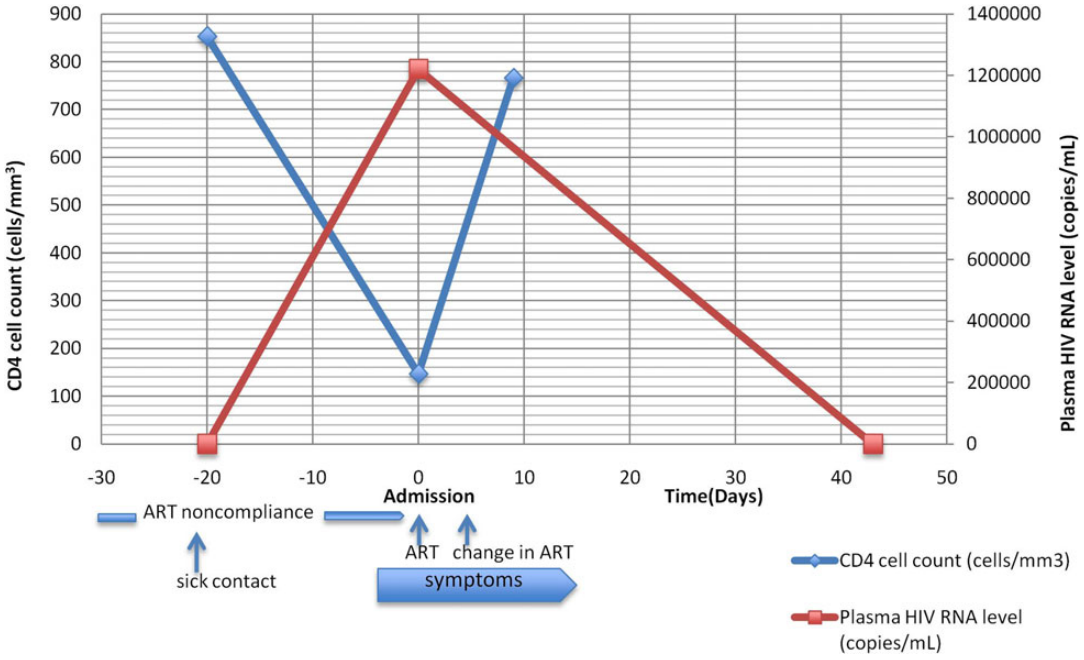

Figure 1. Temporal trends in CD4 cell count and human immunodeficiency virus (HIV) RNA. Abbreviation: ART, antiretroviral therapy.

diarrhea, fatigue, fever and/or night sweats, dyspnea, nausea, and vomiting after TI [5].

The genotyping of HIV-1 (subtype B) found no mutation in our patient, although the test was conducted under drug selection pressure while on lamivudine/zidovudine for at least 4 days after admission. Unfortunately, previous genotyping test and CD4 nadir count were not available because the patient had excellent virologic control and maintained CD4 count at approximately 800 for 16 years before admission. It was unlikely that the patient contracted a new HIV strain with no identified risk factors. The absence of mutations may be explained by possible full nonadherence or variant wild-type virus gaining viral fitness in relatively short period of time. After the patient's ART regimen was changed (TDF/FTC, dolutegravir) and upon follow up after discharge, viral replication was suppressed with pVL becoming undetectable in 6 weeks (Figure 1).

Our patient's remote history of travel to Africa prompted us to rule out other possible infectious etiologies. The lack of alternative infectious diagnoses along with dramatic increase in pVL, marked decrease in CD4 cell counts, and clinical response to ART support our diagnosis of acute HIV syndrome. It is not clear whether history of contacting a sick child with viral illness or recurrent genital herpes may have contributed to her viral rebound phenomenon. In the absence of ART, influenza and other routine immunization have been shown to transiently activate HIV replication [2]. Her history with sick contact and onset of acute HIV syndrome may be coincidental; however, this temporal relationship may suggest perturbation of the immune system triggered by other common viruses in the setting of nonadherence to ART.

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Potential conflict of interest. Both authors: No reported conflicts.
Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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