

## Hemophagocytic Lymphohistiocytosis: An Unusual Initial Presentation of Acute HIV Infection

### To the Editor:

Hemophagocytic lymphohistiocytosis (HLH) has been described in HIV-infected patients who developed opportunistic infections or malignancies.<sup>1,2</sup> The hypercytokinemia triggered by malignancy or coinfection with human herpesvirus-8 or other opportunistic infections and the generalized defects in T-cell and natural killer (NK) cell cytotoxicity in HIV-infected patients are

characteristic immunologic features of HLH,<sup>3,4</sup> which explains the predisposition to HLH in patients with HIV infection. HLH could also be one of the manifestations of acute HIV infection,<sup>5-8</sup> although it has rarely been described to date.<sup>9</sup> Here, we present 3 cases of HLH as the initial presentation of acute HIV infection and review the literature.<sup>5-8</sup> Detailed clinical characteristics of the 7 cases of HLH of patients with acute HIV infection, including our 3 cases, are shown in Table 1.

Of the 7 patients diagnosed with acute HIV infection and HLH, 4 were homosexual men. Their median age was 27 years (range: 18–31 years). The presenting symptoms of acute HIV infection were fever (100%), generalized or local-

ized lymphadenopathy (100%), sore throat (86%), and skin rashes (71%). Hepatomegaly or splenomegaly (100%) was detected by physical examination or image studies (see Table 1). Five patients had oroesophageal candidiasis. Severe complications were found in 3 patients: 2 patients developed encephalopathy;<sup>6,7</sup> 1 had renal failure, acute pancreatitis, and pancreatic panniculitis;<sup>7</sup> and 1 had blurred vision.<sup>8</sup> Laboratory data showed leukopenia (median value = 2200 cells/ $\mu$ L, range: 1400–10,085 cells/ $\mu$ L), anemia (median value = 12.2 g/dL, range: 9–15.7 g/dL), thrombocytopenia (median value = 175,000 cells/ $\mu$ L, range: 99,000–184,000 cells/ $\mu$ L), hyperferritinemia (median value = 10,817.5 ng/dL, range: 2227–29,893 ng/dL), and elevated

**TABLE 1.** Clinical Characteristics of 7 Patients With Acute HIV Infection and HLH

References	Age (y)/Sex	Fever	HM/SM	WBC (g/ $\mu$ L)	Hb (g/dL)	Plt (K/ $\mu$ L)	TG (mg/dL)	Ferritin (ng/mL)
5	27/M	+	++	10,085	10.9	194	NA	NA
6	28/F	+	+/-	1400	12.2	70	NA	NA
7	31/M	+	+/-	1600	9.0	94	NA	NA
8	18/M	+	-/+	2800	14.7	90	184	17,010
PR	31/M	+	-/+	5850	11.3	12	182	4625
PR	23/M	+	-/+	2200	13	102	168	2227
PR	25/M	+	++	1670	15.7	59	99	29,893

  

References	LDH (U/L)	Biopsy Site*	CD4 cells/ $\mu$ L	CD8 cells/ $\mu$ L	PVL log <sub>10</sub> copies/mL	Treatment	Complications
5	NA	LN	500	NA	NA	NA	Nil
6	1218	BM	NA	NA	NA	Acetaminophen, ketoconazole	Oral candidiasis, encephalopathy
7	NA	LN	300	NA	NA	Steroids, fluconazole	Esophageal candidiasis, acute renal failure, acute pancreatitis, pancreatic panniculitis, encephalopathy
8	3830	BM/LN	63	NA	5.72	IVIG, antibiotics	Blurred vision
PR	989	BM	324	1617	5.88	IVIG, antibiotics, steroids, fluconazole	Oral candidiasis
PR	1483	BM	194	1302	5.88	IVIG, fluconazole	Oral candidiasis
PR	4769	BM	101	364	5.88	Antibiotics, fluconazole	Oral candidiasis

BM, indicates bone marrow; F, female; HM/SM, hepatomegaly/splenomegaly; Hb, hemoglobin; IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; LN, lymph node; M, male; NA, not available; PR, present report; Plt, platelet; PVL, plasma HIV-RNA load; TG, triglyceride; WBC, white blood cell count; -, negative; +, positive.

\*The biopsy site where hemophagocytosis was demonstrated.

lactate dehydrogenase (LDH) levels (median = 1483 U/L, range: 989–4769 U/L). The CD4 lymphocyte counts of the 7 patients were low at the time acute HIV infection was diagnosed, with a median count of 247 cells/ $\mu$ L (range: 63–500 cells/ $\mu$ L), and the median CD8 count was 1302 cells/ $\mu$ L (range: 364–1617 cells/ $\mu$ L). Plasma HIV RNA load was available in 4 patients, with a median value of 5.88 log<sub>10</sub> copies/mL by reverse transcriptase–polymerase chain reaction (RT-PCR; range: 5.72–5.88 log<sub>10</sub> copies/mL). Histiocytosis with hemophagocytosis was demonstrated in biopsies of the bone marrow or lymph nodes.

Acute HIV infection has long been a difficult diagnosis to make because of its nonspecific symptoms.<sup>9</sup> Compared with the patients previously described and reviewed, who had opportunistic infections or malignancies at the diagnosis of HLH,<sup>1,2</sup> all 7 patients with acute HIV infection and HLH had fever, generalized or localized lymphadenopathy, and hepatomegaly or splenomegaly at presentation. Less hypertriglyceridemia and higher CD4 counts were noted. All patients survived after supportive care was instituted. Although some of them had received immunomodulating agents, such as intravenous immunoglobulin (3 patients) and steroids (2 patients), the benefit of these agents in the treatment of HLH associated with acute HIV infection remains unclear. Our experience and our review of the literature suggest that hemophagocytosis could be one of the initial presentations of acute HIV infection.

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## Response to the Comparison of Generic Zidovudine Plus Lamivudine (Cipla, Duovir) and the GlaxoSmithKline Brand (Combivir) Tablets

### To The Editor:

With the growing prevalence of AIDS in Asian and sub-Saharan African countries, it is imperative that pharmaceutically pure cost-effective treatment regimens are made available for patients in resource-poor countries. Recently, Henry et al<sup>1</sup> analyzed, in a single capsule, the content of lamivudine (3TC) and zidovudine (AZT) in 2 brands of lamivudine 150-mg/zidovudine 300-mg combination tablets, Combivir (GlaxoSmith-

Kline, Lot 1ZP2346) and Duovir (Cipla, Lot C10237). The study utilized a validated high-performance liquid chromatography (HPLC) assay described by Kakuda et al<sup>2</sup> to determine the content uniformity of 3TC and AZT. The study concluded that although the content of AZT was within the tolerance limits, the content of 3TC in Duovir tablets (112%) was slightly higher than the specified tolerance limits (90%–110%).

Utilizing an in-house validated HPLC method (registered with World Health Organization), the content of 3TC and AZT in the same lot of Duovir tablets as tested by Henry et al<sup>1</sup> was found to be 99.3% and 97.4% for 3TC and AZT, respectively (data on file, Cipla, 2001). Therefore, the content of 3TC and AZT was within the specified tolerance limits of 90% to 110%. The discrepancy in results presented herein and by Henry et al<sup>1</sup> may be primarily a result of differences in analytic methodologies. In addition, we would like to clarify that Combivir and Duovir are formulated as tablets and not as capsules, as mentioned by Henry et al.<sup>1</sup> Furthermore, the study by Henry et al<sup>1</sup> utilized only a single tablet in its analysis. Based on guidelines set forth in United States Pharmacopoeia for content uniformity, in case of analysis of a single tablet, the content of the active pharmaceutical ingredient may vary from 85% to 115% of the label claim (USP27-NF22). Moreover, to claim the content of the active ingredient to be within 90% to 110%, at least 5 intact tablets need to be analyzed (USP27-NF22). In conclusion, we wish to reiterate that the content uniformity of 3TC and AZT in Duovir tablets is clearly within the tolerance limits.

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## Eradication of Vertical Transmission of HIV: A Response to Mayaux et al

### To the Editor:

While the incidence of neonatal transmission of HIV has declined significantly in the United States since the introduction of zidovudine, the annual number of new cases of horizontally transmitted HIV remains unchanged.<sup>1</sup> Among women in the United States, the incidence of HIV infection continues to rise. In addition, due to advancements in treatment of HIV with highly active antiretroviral therapies, HIV-infected women are living longer and healthier and, therefore, with greater opportunity to reproduce.

Most women with HIV infection in the United States are able to obtain prenatal and HIV care to minimize the risk of transmitting the virus to their newborn. As a result, vertical transmission rates in most American centers are <1–2%.<sup>1</sup> Efforts to reduce mother-to-child transmission of HIV have been enormously successful, allowing a paradigm shift from reduction to eradication of vertical transmission. Tactics have not shifted accordingly. Is it possible that the kinds of interventions used to effect reduction may not be sufficient for achieving eradication? Perhaps the minority of women who were not reached by a current strategy for reducing vertical transmission require a different kind of message or attention.

In the November 2003 issue of the *Journal of Acquired Immune Deficiency*

*Syndromes*, Mayaux et al<sup>2</sup> reported on a French observational study of 2167 HIV-seropositive mothers who knew their HIV status, most of whom received antiretroviral prophylaxis and gave birth to HIV-seronegative babies (93.7%). A small number of these mothers (4.3%) did not get perinatal treatment and transmitted HIV at a much higher rate (17%). The authors conclude that “earlier screening and focusing on a small subgroup of socially marginalized women” could further reduce the vertical transmission of HIV.

We write with affirmation of the conclusion of Mayaux et al, based on recently completed work in Chicago that identified and consulted with a subgroup of extremely socially marginalized mothers with HIV with the goal of elucidating new strategies for eradication of mother-to-child transmission. In Chicago, public health data estimate that approximately 125 babies are born each year to mothers infected with HIV. At least 32 babies have been perinatally infected in Chicago since 1997.

We identified 15 mothers at high risk for vertical transmission who might not have been reached by current prevention strategies. These mothers knew their HIV status and gave birth to at least 2 children during the era of combination antiretroviral therapy and did not get appropriate perinatal treatment. They were identified through a Department of Children and Family Services (DCFS) database and were all women who had had children removed from their custody.

In addition to their involvement with child welfare services, these mothers shared common and overlapping institutional histories including contact with substance abuse and treatment programs, the mental health system, and the criminal justice system. The mothers we interviewed demonstrated characteristics of extreme social marginalization, as envisioned by Mayaux et al and as documented in other studies such as those discussed by Gilbert and Wright.<sup>3</sup> Nearly all of the study participants were younger than age 35, infrequently if ever em-

ployed, never married, and living well below the U.S. poverty line. All but one of the mothers identified as African American. All reported teen pregnancies followed by dropping out of school; none had graduated from high school. Common life circumstances included unstable childhoods, lack of parental involvement, physical and sexual abuse, childhood involvement with DCFS, homelessness, and trading sex for money, drugs, and shelter. Psychological conditions including depression, denial of HIV status, and substance dependence constituted the norm. When asked about social support and friends, nearly every single woman reported that she had no friends.

On average, these mothers had given birth to  $\geq 4$  children (2–12 range), at least twice the average number of babies born to women in the general U.S. population, with a perinatal transmission rate after 1997 of approximately 15% (almost equal to the 17% rate reported by Mayaux et al). Compare this to a 4% transmission rate among all HIV-positive mothers nationally, and a <1% rate among mothers receiving HIV treatment in the United States. These mothers tell the stories of Mayaux’s “small subgroup of socially marginalized women” who, in order to be reached, require special focus.

We need to understand these women further.<sup>4</sup> As we continue our work to analyze the lessons learned from these mothers, one conclusion emerges as crystal clear. Traditional medical strategies aimed at prevention have already failed these women. Earlier detection must be reframed. The mothers we interviewed avoided prenatal care due to distrust in medical institutions and fear that their newborns would be reclaimed. They withheld disclosure at the time of delivery because the perceived risk of stigma and loss of privacy overwhelmed them. Wider and earlier testing of HIV will not suffice for earlier detection. Creating an environment in which HIV-positive mothers can disclose their status and feel cared for will allow them

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to avail themselves of treatments that they largely acknowledge to be of benefit.

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## ERRATUM

The guest editor for Supplement 2, *Prevention Interventions With Persons Living With HIV/AIDS: Challenges, Progress, and Research Priorities*, Volume 37, October 1, 2004, is Christopher M. Gordon.