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REVIEW ARTICLE

A Review of Hemophagocytic Lymphohistiocytosis in Patients With HIV

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We provide an elaborate review of cases published between January 2005 and April 2021 on hemophagocytic lymphohistiocytosis (HLH) in HIV patients. Seventy articles describing 81 adult patients (age ≥19 years) were included. The median age was 40 years, and 78% were males. Only 65% were known to have HIV before presentation. CD4 count was ≥200 cells/mm^3 in 23%, and HIV viral load was <200 copies/mL in 41%. The lack of meticulous reporting of ≥5 of 8 criteria for HLH diagnosis was evident in a third of cases. At least 1 infectious agent—other than HIV—was believed to trigger HLH in 78% of patients. The most common were Epstein-Barr virus (26%), human herpesvirus 8 (21%), and *Histoplasma capsulatum* (17%). Sixty percent survived. Among those, 93% received treatment for identified secondary trigger(s), while 51% received HLH-directed therapy. There was significant heterogeneity in the treatment regimens used for HLH.

Keywords. AIDS; hemophagocytosis; HIV; lymphohistiocytosis.

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening syndrome driven by unregulated hyperactive T-lymphocytes and macrophages causing hematopoietic cell phagocytosis and excessive inflammatory cytokine release [1, 2]. It can be genetic (primary HLH) or acquired (secondary HLH) [1, 2]. The latter is secondary to immunological dysregulation induced by isolated pathological events—herein referred to as "secondary triggers," such as infections, malignancies, or autoimmune conditions [2]. The true incidence and prevalence of HLH are difficult to estimate as the diagnosis is often missed due to lack of clinical suspicion or knowledge about the disease [3].

HLH can present with various clinical signs and symptoms, including fevers, jaundice, lymphadenopathy, rash, body swelling, neurologic deficits, and hepatosplenomegaly [1]. Common laboratory findings include cytopenia, liver synthesis dysfunction, and elevated level of ferritin, triglycerides, and serum transaminases. Coagulopathy can also be seen. Cerebrospinal fluid analysis (CSF) can demonstrate high proteins and pleocytosis. Other findings include low natural killer cell activity and high soluble interleukin-2 receptor (CD25) in both serum and CSF [1]. Histopathology may show accumulation of lymphocytes and activated macrophages from various sites [4]. However, absence of hemophagocytic activity on histopathology does not rule out HLH [1, 2].

The diagnosis of HLH requires a positive genetic workup or the presence of at least 5 clinical and laboratory criteria defined by the Histiocyte Society [1]. HLH has a poor overall prognosis even with appropriate therapy [5, 6]. The overall survival at 42 months was only 34% in a previous series [7]. A more fulminant course of HLH may occur in HIV-positive patients [8]. This may be explained by the higher rate of HLH triggers, including infections and malignancies in this patient population [8].

Prospective studies addressing the diagnosis and treatment of HLH have focused mostly on pediatric patients [1, 9]. We are not aware of clinical trials in patients with HLH and HIV, and large observational analytic or descriptive studies in this population remain scarce. The aim of our paper is to provide a concise review on the natural history of HLH in patients with HIV, with a focus on published case reports and small case series.

METHODS

We searched PubMed to identify cases of HLH diagnosed in adult patients living with HIV (age ≥19 years) published between January 2005 and April 2021. The search was performed in May 2021. We used the following search terms: HIV, human immunodeficiency virus, AIDS, acquired immunodeficiency syndrome, HLH, hemophagocytic lymphohistiocytosis, hemophagocytic syndrome, and hemophagocytosis. No search

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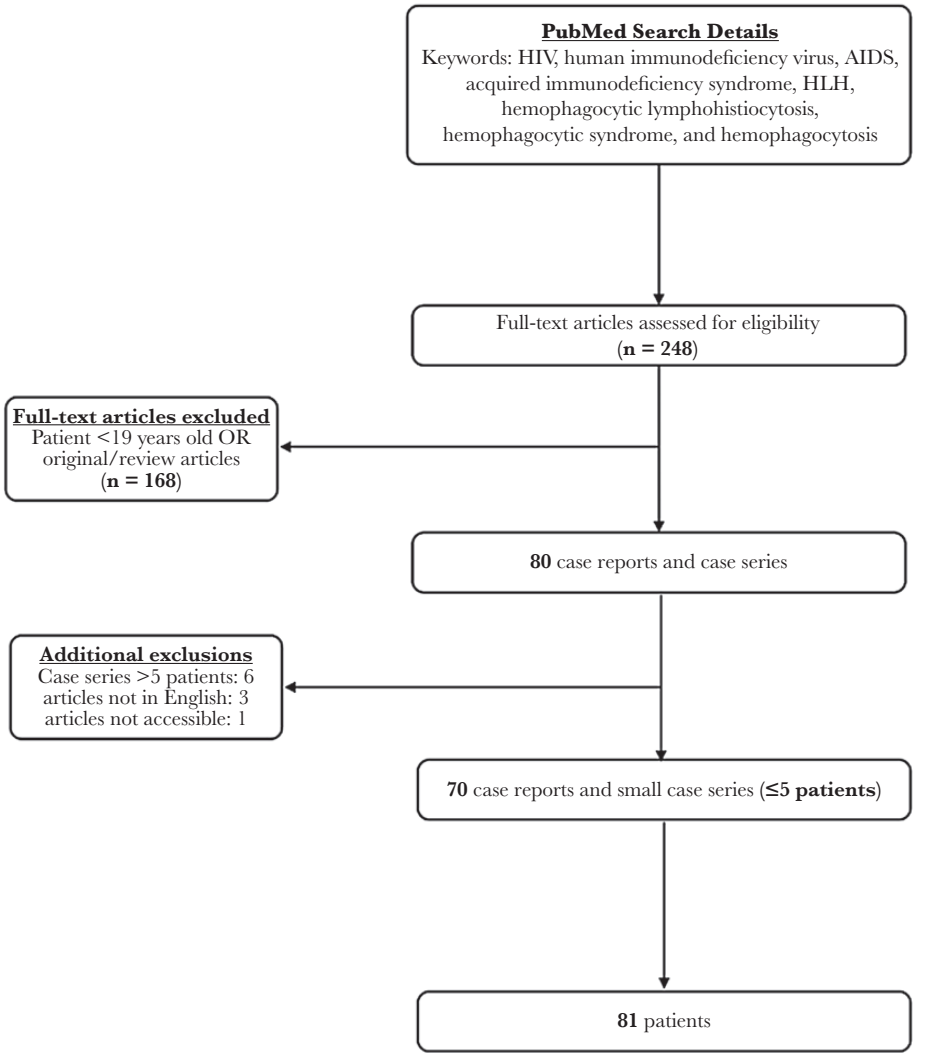
filters were used except for publication date. Our search yielded 248 articles, which were screened for eligibility. We included only case reports and small case series describing <5 patients. We excluded review articles, articles describing patients age <19 years, articles written in languages other than English, and cases in which the patients were not infected with HIV. We also excluded case series describing >5 patients as these often had limited information per case and could not be used; a summary of excluded case series can be found in Supplementary Table 1. A total of 70 articles were included in the final review. Two reviewers (H.T. and A.K.) independently screened the titles and/or abstracts of all studies, reviewed all included articles, and collected data including patient baseline characteristics, clinical and laboratory findings, treatment, and outcomes. Discordances were resolved through discussion among group members. Figure 1 provides a schematic workflow for our search.

DEFINITIONS

We used diagnostic criteria published by the Histiocyte Society to define HLH. The first set of diagnostic guidelines were presented in 1991 [10] and were later revised in the HLH-2004 document (Supplementary Table 2) [1].

We screened patients for immune reconstitution inflammatory syndrome (IRIS). We considered IRIS in patients presenting with systemic inflammatory syndrome shortly after starting antiretroviral therapy (ART) who had >1 $\log_{10}$ copies/mL decrease from pre-ART HIV viral load at time of presentation [11].

Baseline HIV status was defined by HIV viral load (VL), CD4 T-cell count, and ART around the time of HLH diagnosis. HIV status at presentation was considered "uncontrolled" if (1) patients were previously known to have HIV but were not receiving ART, (2) patients had poor response to ART (ie, HIV VL ≥200 copies/mL or CD4 T-cell count <200



Country of publication	
USA	31
Japan	6
China	4
Belgium	3
France	3
India	3
UK	3
Portugal	2
Spain	2
Brazil	1
Canada	1
Germany	1
Greece	1
Israel	1
Italy	1
Mexico	1
Nigeria	1
Saudi Arabia	1
South Africa	1
South Korea	1
Switzerland	1
Turkey	1

Figure 1. Flow diagram of literature review methodology used to identify all PubMed indexed cases of HLH in HIV patients reported from January 2005 until April 2021. Abbreviation: HLH, hemophagocytic lymphohistiocytosis.

cells/mm^3), or (3) patients were diagnosed with HIV for the first time at presentation. HIV at presentation was considered "controlled" if patients were on already on ART and met all of the following 3 criteria: (1) documented low-level viremia at presentation (ie, HIV VL <200 copies/mL), (2) documented CD4 T-cell count ≥200 cells/mm^3 at presentation, and (3) levels of HIV VL and CD4 T-cell count considered stable rather than a response to recent ART initiation (such as seen with IRIS).

All conditions or diseases other than HIV that were concomitantly diagnosed and reported during HLH workup were considered by reviewers as possible secondary trigger(s) if thought significant enough to have elicited immunological dysregulation leading to HLH.

RESULTS

Our literature review using the PubMed search engine resulted in 70 articles. Fifty-eight articles (83%) originated from developed countries. A data summary for all captured cases in our review is provided in Supplementary Table 3.

Clinical Presentation and Laboratory Findings

A total of 81 patients with HIV and presenting for HLH were described in the included articles [8, 12–80]. The median age of patients (interquartile range [IQR]) was 40 (33–48) years, and the majority were men (63/81; 78%). The clinical syndrome of HLH varied widely from acute progressive illness to subacute or chronic wasting syndrome. The duration of symptoms ranged from 1 to 330 days before presentation, with a median (IQR) of 18 (7–30) days. Overall, only 64% (52/81) had explicit documentation of ≥5 out of 8 HLH criteria for diagnosis. This includes patients meeting diagnostic criteria at presentation or subsequently on serial laboratory testing. The remaining 29 patients were mostly diagnosed with HLH based on positive tissue pathology, but a clear documentation of ≥5 out of 8 criteria was not completed (Supplementary Table 4).

Three laboratory criteria were almost universally present when tested: fever (80/81; 99%), ferritin level ≥500 µg/L (64/64; 100%), and low natural killer (NK) cell activity (10/10; 100%) (Table 1). In total, 87% (65/81) patients had evidence of hemophagocytosis in bone marrow. In 5 of these patients, bone marrow analysis was initially negative for hemophagocytosis but turned positive on subsequent evaluation.

Other laboratory abnormalities not included in the HLH diagnostic criteria were also frequently encountered and signified multiorgan damage (Supplementary Table 5). Most patients had evidence of hepatic and renal injury. When measured, a total bilirubin of >1.2 mg/dL and aspartate transaminase (AST) and alanine transaminase (ALT) of ≥40 U/L were seen in 77% (17/22), 94% (31/33), and 88% (36/41), respectively. Notably, AST was higher than ALT in 77% (23/30) of cases, and the AST/ALT ratio was ≥2:1 in 60% (18/30) of cases.

Table 1. Patient Clinical/Laboratory Features and Outcomes

Features	No. Positive/No. Tested	% Positive
Fever, °C	80/81	99
Splenomegaly	52/71	73
Met cytopenia criteria	53/70	76
Ferritin ≥500 µg/L	64/64	100
Triglycerides ≥265 mg/dL	34/47	72
Fibrinogen ≤1.5 g/L	10/25	40
Low NK cell activity	10/10	100
sCD25 ≥2400 U/mL	21/23	91
Positive biopsy for HLH	70/80	88
Positive BM aspirate/biopsy	65/75	87
Positive LN biopsy	5/11	46
Positive liver biopsy	6/8	75
HIV viral load		
<200 RNA copies/mL	26/63	41
≥200 RNA copies/mL	37/63	59
CD4+		
<200 cells/mm^3	58/75	77
≥200 cells/mm^3	17/75	23
Outcomes[a]		
Relapse	3/28	11
Cure	49/81	60
Death	32/81	40

Abbreviations: BM, bone marrow; HLH, hemophagocytic lymphohistiocytosis; LN, lymph node; NK, natural killer.

[a]For relapsed patients (n = 3), only the outcome of their last hospitalization was recorded.

At the time of presentation, 65% (53/81) of all patients were already known to have HIV. The median time from their HIV diagnosis to developing HLH (IQR) was 1 (0.3–6.0) year. ART was queried in 51 of these patients, 69% (35/53) of whom were actively receiving ART before developing HLH. On the other hand, 35% (28/81) of all patients were not previously known to have HIV, and HLH was the presenting syndrome leading to their HIV diagnosis; 32% (9/28) were considered to have acute retroviral syndrome.

HIV VL and CD4 T-cell count were reported at presentation in 78% (63/81) and 93% (75/81) of patients, respectively (Table 1). Both tests were reported simultaneously in 77% (62/81) of patients. Based on our definition, HIV was considered controlled at presentation in 12% (10/81) and uncontrolled in 88% (71/81). The CD4 T-cell count ranged from 0 to 604 cells/mm^3, and the HIV viral load varied from undetected to >1 000 000 000 RNA copies/mL.

HLH Triggers

In 15% (12/81) of patients, no diagnosis other than HIV was identified during workup for HLH. All patients in this group had uncontrolled HIV at presentation. Acute retroviral syndrome was considered in 42% (5/12) and IRIS in 8% (1/12). For those without acute retroviral syndrome or IRIS (6/12), it

remains unknown whether HLH was triggered by HIV alone or some undiagnosed secondary trigger.

In contrast, 1 or more conditions other than HIV were diagnosed in the remaining 85% (69/81) of patients and might have served as the secondary trigger(s) for HLH. These conditions can be categorized into infections, viral-induced malignancies, and primary malignancies not induced by virus. Table 2 provides a list of such reported conditions. Note that most patients had multiple possible triggers. Infectious pathogens other than HIV were present in 78% (63/81) of all patients. The most common were viral and fungal pathogens, seen in 53% (43/81) and 24% (20/81) of patients, respectively. Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8) were the most frequently identified viruses, and both were often associated with neoplasms or lymphoproliferative disorders. Viral pathogens were equally present in patients with different HIV VLs and CD4 T-cell counts. Most fungal infections presented as invasive disease and were more often found in patients with CD4 T-cell counts <200 cells/mm^3. The most reported form of fungal disease was disseminated histoplasmosis, which was present in 70% (14/20) of patients diagnosed with fungal infection. While bacterial infections were collectively common, no single bacterial pathogen was commonly reported.

Noninfectious secondary triggers included primary malignancies not induced by virus in 11% (9/81) of patients. In addition, 2 patients presented with HLH during pregnancy. In 1 patient, pregnancy was considered a possible trigger, while in the other patient, a concomitant diagnosis of malaria was made.

IRIS was considered along with HLH in 19% (15/81) of patients. These patients were known to have HIV and were started on ART shortly before presenting with a systemic inflammatory syndrome. However, only 10 patients had a documented decline of >1 $\log_{10}$ copies/mL from pre-ART HIV VL at the time of presentation for HLH. The median duration from ART initiation to HLH (IQR) was 1 (0.5–3) month. For the remaining 5 patients, the pre-ART VL was not reported.

Finally, among patients who had controlled HIV at presentation, secondary triggers mainly involved EBV- and/or HHV-8-induced neoplasms or lymphoproliferative disease (6/10; 60%), primary malignancies not induced by virus (2/10; 20%), systemic fungal infections (2/10; 20%), and pregnancy (1/10; 10%).

Therapeutic Approach and Outcomes

Sixty percent (49/81) of patients survived and were discharged, while 40% (32/81) died. Death occurred in 40% (4/10) of patients considered to have controlled HIV at presentation and 39% (28/71) of those with uncontrolled HIV.

At least 1 secondary trigger was identified in 84% (41/49) of those who survived and 88% (28/32) of those who died. When compared with survivors, patients who died had higher prevalence of IRIS and primary malignancies not induced by virus: 2% (6/49) vs 28% (9/32) and 4% (2/49) vs 22% (7/32), respectively (Table 2). Some virally induced neoplasms, such as EBV-related lymphoma, were also more common in those who died: 10% (5/49) vs 25% (8/32), respectively. On the other hand, more cases of invasive fungal infections were reported in those who survived: 31% (15/49) vs 16% (5/32), respectively. All cases considered to have acute retroviral syndrome (9/81) at the time of HLH survived. Most of them (5/9; 56%) had no diagnosis other than HIV, and all were cured after starting treatment for HIV.

ART was provided during HLH in 84% (41/49) of survivors (Table 3). In 5 survivors diagnosed with disseminated histoplasmosis as possible triggers, ART initiation was deferred until acute illness subsided. In the group of patients who died, 47% (15/32) received ART during HLH, while for the other half ART management was not reported.

Among patients diagnosed with secondary triggers, 75% (52/69) received targeted therapy for triggers (Table 3). This included 93% (38/41) of survivors diagnosed with secondary triggers. In the group of patients who died, only 50% (14/28) were treated for triggers. For the remaining 14 patients from this cohort, 14% (2/14) deteriorated rapidly and opted for comfort care as opposed to treatment, and 36% (5/14) had delayed diagnosis at time of autopsy.

HLH-directed therapy was provided in 60% (49/81) of all patients with HLH (Table 3). A smaller subset of survivors received HLH-directed therapy as compared with patients who died: 51% (25/49) vs 75% (24/32), respectively. HLH-directed therapy was mostly provided in patients with viral-induced neoplasms (20/26; 77%) and other primary malignancies not induced by virus (6/9; 67%). It was infrequently used in patients with treatable infections such as systemic fungal infections (7/20; 35%), bacterial infections (5/12; 42%), and parasitic infections (2/4; 50%). HLH-directed therapy was also used in 58% (7/12) of those with no diagnosis other than HIV, 44% (4/9) of patients with acute retroviral syndrome, and 80% (12/15) of patients with IRIS.

In 37% (18/49) of patients receiving HLH-directed therapy, the regimen consisted of steroids alone and was likely suboptimal (Table 4). In addition, many cases did not specify the type or duration of HLH-directed therapy. The most-used regimen was etoposide in combination with steroids. Of 19 patients who received etoposide, as monotherapy or combination, 47% (9/19) died.

Follow-up postdischarge was documented for 57% (28/49) of survivors. The median duration of follow-up (IQR) was 5.5 (4–9) months. After cure, only 3 patients had relapse of HLH at 2 weeks, 3 months, and 8 months (Supplementary Table 2).

DISCUSSION

This review provides an elaborate description of over a decade and a half worth of published cases on HLH in HIV and highlights the intricate course of this morbid entity.

Table 2. Distribution of Secondary Triggers Stratified by Outcome

	Total (n = 81)	Cure (n = 49)	Death (n = 32)
Median age (Q1–Q3), y	40 (33–48)	36 (31–45)	46 (39–53)
Known HIV before presentation, No. (%)	53 (65)	24 (49)	29 (91)
Median CD4 (Q1–Q3) cells/mm^3	73 (17–157)	66 (17–138)	76 (16–202)
Acute retroviral syndrome, No. (%)	9 (11)	9 (18)	–
Immune reconstitution inflammatory syndrome, No. (%)	15 (19)	6 (12)	9 (28)
No HLH trigger other than HIV, No. (%)	12 (15)	8 (16)	4 (13)
Patients with viral infection/disease, No. (%)	43 (53)	25 (51)	18 (56)
EBV related, No. (%)	21 (26)	9 (18)	12 (38)
• Viremia w/out lymphoma	9 (11)	6 (12)	3 (9)
• With associated lymphoma	12 (15)	5 (10)	8 (25)
HHV8 related, No. (%)	17 (21)	11 (22)	6 (19)
• Viremia w/out KS, MCD, lymphoma	1 (1)	1 (2)	
• With KS, MCD, or lymphoma	16 (20)	10 (20)	6 (19)
▪ KS	11 (14)	5 (10)	6 (19)
▪ MCD	6 (7)	4 (8)	2 (6)
▪ Lymphoma	4 (5)	2 (4)	2 (6)
CMV related, No. (%)	6 (7)	6 (12)	–
• Viremia w/out organ disease	5 (6)	5 (10)	–
• CMV with organ disease	1 (1)	1 (2)	–
HSV related, No. (%)	3 (4)	2 (4)	1 (3)
• Viremia w/out organ disease	1 (1)	1 (2)	–
• HSV with organ disease	2 (2)	1 (2)	1 (3)
Other viral related, No. (%)	2 (2)	1 (2)	1 (3)
• Acute hepatitis B	1 (1)	–	1 (3)
• Parvovirus B19 AA	1 (1)	1 (2)	–
Patients with invasive fungal infection, No. (%)	20 (24)	15 (31)	5 (16)
Cryptococcus neoformans, meningitis, No. (%)	1 (1)	–	1 (3)
Aspergillus fumigatus, pulmonary, No. (%)	1 (1)	–	1 (3)
Histoplasma capsulatum, disseminated, No. (%)	14 (17)	13 (27)	1(3)
Penicillium marneffei, disseminated, No. (%)	1 (1)	1 (2)	–
Pneumocystis jirovecii pneumonia, No. (%)	2 (2)	1 (2)	1 (3)
Systemic fungal infections (NS), No. (%)	2 (2)	–	2 (6)
Patients with bacterial infection, No. (%)	12 (15)	7 (14)	5 (16)
Bacteremia, No. (%)	2 (2)	2 (4)	–
Bacterial pneumonia, No. (%)	1 (1)	–	1 (3)
Ehrlichia chaffeensis, No. (%)	1 (1)	–	1 (3)
Bartonella henslae, No. (%)	1 (1)	1 (2)	–
Clostridioides difficile, colitis, No. (%)	1 (1)	1 (2)	–
Treponema pallidum, No. (%)	1 (1)	1 (2)	–
Mycobacterium tuberculosis complex, No. (%)	3 (4)	1 (2)	2 (6)
Mycobacteria avium complex, No. (%)	3 (4)	2 (4)	1 (3)
Patients with parasitic infection, No. (%)	4 (5)	3 (6)	1 (3)
Toxoplasma gondii, disseminated, No. (%)	1 (1)	–	1 (3)
Leishmania species, visceral, No. (%)	2 (2)	2 (4)	–
Plasmodium falciparum, No. (%)	1 (1)	1 (2)	–
Patients with primary malignancy, No. (%)	9 (11)	2 (4)	7 (22)
Lymphoma, No. (%)	8 (10)	2 (4)	6 (19)
Multiple myeloma, No. (%)	1 (1)	–	1 (3)

Values in parentheses represent column percentages.

Abbreviations: AA, aplastic anemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; HSV, herpes simplex viruses; KS, Kaposi sarcoma; MCD, multicentric Castleman's syndrome.

Most cases described young and middle-aged adult men with a diagnosis of HIV (median duration, 1 year) who were receiving antiretroviral therapy. Only a minority had controlled HIV (median CD4 T-cell count, 73 cells/mm^3), which implies that HLH seems to develop more frequently in patients with chronic uncontrolled HIV infection. This is echoed by a retrospective study of 58 patients with HIV where the median duration of HIV infection was 4 years and the median CD4 count

Table 3. Baseline HIV Status and Therapeutic Approach in Different Outcome Groups

	Total (n = 81), No. (%)	Cure (n = 49), No. (%)	Death (n = 32), No. (%)
Baseline HIV status			
HIV viral load			
<200 RNA copies/mL	26 (32)	9 (18)	15 (47)
≥200 RNA copies/mL	37 (46)	30 (61)	8 (25)
NR	18 (22)	10 (20)	9 (28)
CD4 count			
<200 cells/mm^3	58 (72)	39 (80) (IRIS = 6)	19 (59)
≥200 cells/mm^3	17 (21)	9 (18) (IRIS = 0)	8 (25)
NR	6 (7)	1 (2) (IRIS = 0)	5 (16)
ART			
1. Yes	56 (69)	41 (84)	15 (47)
• Started	29 (36)	25 (51)	4 (13)
• Resumed	20 (25)	11 (22)	9 (28)
• Adjusted	2 (2)	-	2 (6)
• Delayed until acute illness improved	5 (6)	5 (10)	-
• Stopped	1 (1)	-	1 (3)
2. No	1 (1)	-	1 (3)
3. NR	26 (32)	11 (22)	15 (47)
Secondary trigger identified	69 (85)	41 (84)	28 (88)
Treatment for secondary trigger(s)			
1. Yes	52 (65)	38 (78)	14 (44)
2. No	10 (12)	2 (4)	12 (38)
3. NR	2 (2)	1 (2)	5 (16)
Treatment for HLH			
1. Yes	49 (60)	25 (51)	24 (75)
2. No	17 (21)	23 (47)	6 (19)
3. NR	1 (1)	1 (2)	2 (6)
Treatment for both HLH and secondary trigger(s)	32 (40)	20 (41)	12 (38)

Values in parentheses represent column percentages.

Abbreviations: ART, antiretroviral therapy; HLH, hemophagocytic lymphohistiocytosis; IRIS, immune reconstitution inflammatory syndrome; NR, not reported.

was 91 cells/mm^3 [81], and could partly be explained by the fact that these patients are at increased risk for opportunistic infections, which are directly or indirectly responsible for the development of HLH. In patients with low-level viremia and CD4 T-cell count ≥200 cells/mm^3, it is likely that the immune dysregulation related to HIV (ie, NK and T-cell dysfunction) is playing a role in the development of HLH [81].

The diagnosis of HLH in patients with HIV is challenging and requires a high index of suspicion. This is because various clinical and laboratory abnormalities listed in the diagnostic criteria for HLH can be seen with advanced HIV/AIDS. Moreover, hemophagocytic syndromes can mimic sepsis and other conditions that are often encountered in patients with HIV [82]. We found 2 laboratory tests that were always positive: ferritin ≥500 µg/L and low NK cell activity. Another test with a high positivity rate was soluble CD25 level ≥2400 U/mL. Ferritin may be a quick test to obtain when patients with HIV present with a systemic inflammatory syndrome. While a ferritin level ≥500 µg/L is not specific to HLH [83], HLH should be considered, especially when ferritin levels are significantly elevated. The median ferritin level in our review (IQR) was 14 716 (6347–31 540) µg/L. HLH can be present in up to 14% of patients with ferritin levels >10 000 µg/L based on prior series [83]. NK cell activity and soluble CD25 assays are also great tools to aid in the diagnosis of HLH. However, both tests are not readily available in nonspecialized centers [84] and are expensive, labor-intensive, and time-consuming [85]. In instances where the diagnosis of HLH might not be so evident, resorting to these immunological assays may be necessary.

Hemophagocytic activity in bone marrow was commonly detected in our review. Therefore, when HLH is considered, a histopathologic evaluation should be sought due to its high yield. However, physicians are reminded that the Histiocyte Society does not consider evidence of hemophagocytosis on histopathology as a standalone diagnostic criterion for HLH and that attempts to fulfill at least 5 out of 8 criteria before a diagnosis of HLH is made should be carried out.

Most patients in our review had elevated transaminases. AST/ALT ratio ≥2:1 was commonly detected. This finding is not unusual. In fact, the HScore, which was developed in 2014 to predict a patient's risk of having HLH, included AST level as 1 of 9 other variables; AST level is the only biologic variable that was entirely omitted from the HLH-2004 criteria [86]. A known underlying immunosuppression such as HIV was another variable in that score [86].

Table 4. Therapeutic Approach and Relative Outcomes

	Total (n = 49), No. (%)	HLH-Directed Therapy in Survivors (n = 25), No. (%)	HLH-Directed Therapy in Those who Died (n = 24), No. (%)
Monotherapy			
• Glucocorticoids	18 (37)	9 (36)	9 (38)
• IVIG	1 (2)	1 (4)	-
• Chemotherapy	2 (4)	1 (4)	1 (4)
Combination therapy			
• Glucocorticoids + IVIG	7 (14)	4 (8)	3 (13)
• Glucocorticoids + chemotherapy	14 (29)	5 (20)	9 (38)
• Glucocorticoids + chemotherapy + IVIG	2 (4)	1 (4)	1 (4)
• Chemotherapy + IVIG	1 (2)	-	1 (4)
• Chemotherapy + splenectomy	4 (8)	4 (8)	-
Chemotherapy, not specified	1 (2)		1 (4)
Etoposide-based	19 (39)	10 (40)	9 (38)
Monotherapy	1 (2)	1 (4)	-
+ IVIG	1 (2)	-	1 (4)
+ Glucocorticoids	10 (20)	3 (12)	7 (29)
+ Glucocorticoids + IVIG	1 (2)	1 (4)	-
+ Glucocorticoids + intrathecal methotrexate	1 (2)	1 (4)	-
+ Rituximab + splenectomy	4 (8)	4[a] (16)	-
+ Glucocorticoids + rituximab	1 (2)	-	1 (4)
Anakinra-based	1 (2)	1 (4)	
+ Glucocorticoids	1 (2)	1 (4)	
Cyclosporin-based	2 (4)	-	2 (8)
+ Glucocorticoids	1 (2)	-	1 (4)
+ Glucocorticoids + IVIG	1 (2)	-	1 (4)

Values in parentheses represent column percentages.

Abbreviations: HLH, hemophagocytic lymphohistiocytosis; IVIG, intravenous immunoglobulin; MCD, multicentric Castleman's syndrome.

[a]All of these cases were for MCD.

It is also worth noting that in some cases initial laboratory studies did not reach the cutoffs for positivity proposed by the HLH diagnostic criteria, but subsequent studies did, and HLH was confirmed after documentation of ≥5 out of 8 criteria. Likewise, tissue pathology may initially be negative for hemophagocytosis. This reflects the dynamic nature of HLH and is another example of how, as a rule, the diagnosis of this condition is not always simple and can heavily rely on clinical judgment.

The type of secondary trigger and its early diagnosis and treatment are factors that may affect outcomes in patients with HIV and presenting with HLH (Table 2). More cases of IRIS and malignancies, both viral- and non-viral-induced, occurred in those who died. This contrasts with the higher rates of fungal infections seen in the group of patients who survived. On the other hand, HIV status at presentation did not have a clear impact on outcome. Death occurred in close proportions of patients with controlled and uncontrolled HIV at presentation.

The optimal therapy for secondary HLH remains unclear. There was clear consensus on the initiation or resumption of ART across patients. Most survivors were started or maintained on ART during HLH. Based on these data, physicians are encouraged to initiate ART early during the HLH course in those who are not already receiving ART and to continue ART (or adjust accordingly) in those who are already receiving it. Most patients identified in our review who had secondary triggers received targeted therapy for these triggers. For patients who did not receive therapy for their secondary triggers, this was often due to delayed diagnosis after they had died. In general, if a treatable secondary trigger was identified early during HLH and properly treated, patients seemed to do well even without HLH-directed therapy. For example, all but 1 of the 14 patients with disseminated histoplasmosis included in our review were cured with antifungal therapy, although only 4 recieved HLH-directed therapy. For the 1 patient who died, histoplasmosis was

diagnosed at time of autopsy and so anti-fungals were never administered. A similar statement can be made for patients who had identifiable bacterial and parasitic infections and viral infections without lymphoproliferative disease. And while there is literature supporting the use of dexamethasone, cyclosporine A, and etoposide among other pharmacologic agents in the treatment of HLH [87], many cases in our review did not receive HLH-directed therapy. When HLH-directed therapy was provided, regimens seemed incomplete in most cases (Table 4). Therefore, the poor response to HLH-directed therapy seen in some cases may be due to a suboptimal regimen rather than lack of benefit in secondary HLH. In addition, patients receiving HLH-directed therapy may have presented more severely, prompting the use of such therapy, as opposed to those who did not receive it. For example, HLH-directed therapy was mainly used in patients with no diagnosis other than HIV, including those with acute retroviral syndrome and IRIS, and in patients with both viral- and non-viral-induced malignancies, while it was rarely used in patients with treatable infectious triggers. The role of HLH-directed therapy in patients with HIV and presenting with HLH should be individualized after consulting with specialists in the field of hematology.

Although this review provides the reader with a detailed description of cases of HLH in HIV, the findings are simple observations and should not be used to infer causations or draw conclusions about this patient population. More robust study designs are needed to assess the effects of a known HIV diagnosis or those of treating secondary causes of HLH on outcomes. Patients' individual characteristics, time to diagnosis of HLH, and therapies employed can all affect outcomes differently, but their association with mortality cannot be determined using the information that was displayed. Nevertheless, HLH remains a highly morbid condition particularly in HIV, as shown in this review and in the literature.

CONCLUSIONS

HLH is challenging to diagnose and treat, particularly in patients with HIV. While considerable advances have been made in the diagnosis and prevention of HIV, there are still patients who develop HLH as their initial presentation for HIV. In this review of cases, a series of specific observations were made, some of which may be unique to this study and/or patient population. These observations ranged from variabilities in symptomatology and diagnostic approaches to differences in treatments and were highlighted here in the hope to improve outcomes in vulnerable HIV patients affected by HLH.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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