Haemophagocytic lymphohistiocytosis (HLH) is a syndrome characterised by severe systemic inflammation and abnormal immune activation leading to a cytokine storm which can be fatal. One of the cardinal features of HLH is hyperferritinaemia (ferritin >500 ng/mL). Other features include high fever, cytopenias, hypertriglyceridaemia or hypofibrinogenemia, splenomegaly and haemophagocytosis seen on bone marrow, lymph node or splenic biopsy. Along with high levels of soluble CD-25 and low NK cell activity, these values are used within the 2004 HLH-protocol criteria to diagnose HLH.

HIV and associated opportunistic infections are a common cause of HLH. Furthermore HLH is an important contributor to mortality in people with advanced HIV. Early treatment of the condition with immunomodulatory medications can halt the progression of HLH, and thus prompt recognition is vital. Untreated HLH carries a very high mortality, especially in patients with advanced HIV.

In this study we looked at eight years of patient data at one HIV centre to investigate the recognition, investigation and treatment of HLH in people living with HIV (PLWH).

AIMS / METHODS
We searched the Royal Free Hospital HIV database for any patient admitted between 2008 and 2016 with a ferritin >2500 ng/mL. This higher value was selected on the basis of HIV itself being a recognised cause of elevated ferritin levels. The patients’ electronic results and letters were reviewed to establish whether the five following criteria of HLH-2004 had been measured, and if so, whether the values fulfilled the diagnostic criteria. The other two measurements required by the HLH-2004 guidelines (NK-cell activity and soluble CD-25) were excluded as they were rarely assessed at this centre.

An established diagnosis of HLH is made when five out of the eight criteria are positive. As only six criteria were measured in this population we defined an established diagnosis when four of the six measured criteria were met.

We also identified which other investigations had been sent during the admission to investigate hyperferritinaemia and possible triggers of HLH. This included viral serology, viral PCR, cultures and serum markers of infection. Outcomes measured assessed included intensive care admission, length of stay, death during admission, diagnosis on discharge or death and treatment given.

RESULTS
Over 2008-16 there were 36 PLWH who had a measured ferritin >2500 ng/mL (Table 2). Median ferritin 4,812 ng/mL, range 2,514 - 30,355 ng/mL.

Table 2: Demographics of patients

<table>
<thead>
<tr>
<th>Marker</th>
<th>Result fulfilling HLH-2004 diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>Fever &gt;38 deg C</td>
</tr>
<tr>
<td>Full blood count</td>
<td>Cytopaenia in &gt;2 lines</td>
</tr>
<tr>
<td>Spleen size</td>
<td>Splenomegaly &gt;14cm</td>
</tr>
<tr>
<td>Triglycerides/Fibrinogen</td>
<td>Hypertriglyceridaemia &gt;3</td>
</tr>
<tr>
<td>Biopsy (bone marrow/lymph node/spenic)</td>
<td>Haemophagocytosis</td>
</tr>
</tbody>
</table>

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RESULTS
Of the 36 patients with ferritin >2500 ng/mL, all had their temperature and full blood count measured, 86% had abdominal imaging, 75% had triglycerides or fibrinogen measured and 43% had a relevant tissue biopsy. Figure 1 shows the proportion of values meeting HLH diagnostic criteria:

A variety of different tests were sent for each patient to investigate possible infective triggers of their illness (Table 3).

Of the 14 PLWH who had all six HLH criteria measured, four (29%) fulfilled 4 or more of the diagnostic criteria, suggesting an established diagnosis of HLH (Table 4). Two had haemophagocytosis on bone marrow (50%).

Table 3: Investigations for infective triggers in PLWH and ferritin >2500 ng/mL

Table 4: Details of four PLWH with HLH

Of the other 14 patients, 10 who did not meet HLH diagnostic criteria, had a lower median ferritin level (8,141 ng/mL) and all survived.

CONCLUSION
Despite ferritin being a non-specific marker, when it is significantly elevated in adult PLWH the possibility of HLH should be considered and investigated using a structured set of investigations. In our study only 39% of PLWH with ferritin >2500 ng/mL had all 6 HLH criteria measured.

Measuring the other markers of HLH is important to ensure prompt diagnosis and treatment that may reduce the chance of death. Formulation of a national or local guideline to advise which investigations are required, and when, may be of help to both clinicians and their patients.

This study confirms the high mortality in PLWH with diagnostic criteria for HLH and advanced HIV. Recently, new targeted treatments for HLH have emerged, such as the IL-1 antagonist Anakinra. The increasing availability of more effective treatment options further highlights the importance of early recognition of this condition.