Fever of Unknown Origin in HIV/AIDS Patients

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Fever of unknown origin (FUO) in adults is defined as a temperature greater than 38.3°C (100.9°F) lasting for more than 3 weeks with no obvious source, despite appropriate investigation. The four categories of FUO are (1) classical, (2) nosocomial, (3) immune deficiency–associated, and (4) HIV-related [1], and the differential diagnoses can be subcategorized into infections, malignancies, autoimmune conditions, and miscellaneous causes [2,3]. A thorough history, physical examination, and standard laboratory testing form the basis of the initial evaluation of the patient with FUO, although newer diagnostic modalities play an important role in assessment.

Fever, either continuous or recurrent, is a common finding in patients infected with HIV and is often accompanied by significant morbidity, prolonged hospitalization, and extensive evaluation [4]. Before highly active antiretroviral therapy (HAART) was introduced, patients with HIV experienced FUO with relative frequency, in most cases caused by opportunistic infections, such as tuberculosis, infection with Mycobacterium avium complex (MAC), and in the Middle East and Mediterranean regions of Europe visceral leishmaniasis. The use of HAART has reduced the frequency of HIV-associated FUO, although the etiologic spectrum remains largely

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unchanged [5]. It remains a common problem in those poorer countries where HAART is less universally available. This article provides a review of the causes of FUO in HIV-infected patients and a rational approach to their diagnostic and therapeutic evaluation.

**Definition and epidemiology**

A consensus definition of FUO in the setting of HIV infection is lacking. Many authors use the criteria proposed by Durack and Street [6]: temperature greater than or equal to 38°C (100.9°F) on multiple occasions; fever of greater than or equal to 4 weeks’ duration for outpatients or more than 3 days for inpatients, including at least 2 days’ incubation of microbiologic cultures; and a diagnosis that remains uncertain after 3 days despite appropriate investigation. This definition has remained unchanged in the era of HAART [6]. It has been suggested that this period of 4 weeks proposed by Durack and Street [6] may, however, be too lengthy in the context of immunocompromised individuals, such as those infected with HIV.

FUO in HIV-infected individuals is not uncommon. The range reported in the literature is variable (3.4%–21% in previous studies) [7–10] probably reflecting rigorous inclusion criteria for FUO diagnosis not always being applied, differential inclusion of outpatient and inpatient populations, and the criteria used for admission to hospital and geographic variation. Most case series of HIV-associated FUO include only patients in the pre-HAART era.

Long-lasting fever in HIV with no recognizable cause is characteristic of the more advanced stages of HIV infection, in patients with a profound loss of their CD4+ T lymphocytes, when the inflammatory reaction responsible for the clinical and radiologic focal signs is impaired because of severe immunosuppression. One series reported 77% of FUO-HIV patients having fewer than 100 CD4+ lymphocytes/mm3 and 66% with fewer than 50 [7]. The median CD4+ cell count in previous reports has ranged from 40 to 94/mm3 [7,9–17]. As a consequence, most documented cases were caused by infection (over 72% of cases) with malignancies and drug effects providing the major noninfectious causes, a classification that reflects the classic studies of Petersdorf and Beeson [18].

The spectrum of causes may be affected by prophylactic medication against opportunistic infection, although few reviews record these data. One study documented those patients on prophylaxis, finding that the percentage of patients diagnosed with MAC and receiving rifabutin prophylaxis (27%) was not significantly lower than those with an etiology other than MAC (35%) or no diagnosis (34%). The percentage with *Pneumocystis jiroveci* pneumonia on prophylaxis (40%) was statistically lower, however, than that of patients with another etiology (85%) or no diagnosis (71%) [7,11].

The widespread use of HAART and antimicrobial prophylaxis has dramatically reduced morbidity and mortality in the setting of HIV infection.
caused by a reduction in viral load, an increase in CD4\(^+\) cell counts [12], and a marked decrease in the incidence of opportunistic infection through a maintenance of immune function [8,19]. Pre-HAART, the incidence of MAC and tuberculosis was approximately three and two cases per 100 person years of follow-up, respectively, with a marked decrease in tuberculosis, and to a larger extent MAC, among HIV-patients since the introduction of HAART. A further series found a substantial reduction in the occurrence of bacteremia in HIV-infected individuals in the post-HAART era [20]. It seems, however, that whereas HAART has significantly reduced the frequency of FUO in HIV, it has not dramatically altered its etiologic spectrum [11].

**Causes of HIV-associated fever of unknown origin**

*Mycobacterial infection*

Infectious diseases remain the predominant cause of FUO in HIV-infected persons worldwide, both pre- and post-HAART, accounting for 82.2% and 90.6% in the United States and Europe, respectively [9–12, 14,16,17,21]. These are often infective agents common in the setting of non-immunocompromised hosts, but manifesting clinically as protracted fever in the context of HIV [7]. All series have demonstrated that mycobacterial infection is the most common cause of FUO in the setting of HIV infection. *Mycobacterium tuberculosis* is the primary cause of FUO in HIV worldwide, especially in areas of high prevalence, such as southwest Europe and developing countries. The global HIV epidemic has created a large population of individuals, including children, who are highly susceptible to disease from *M* tuberculosis and it is estimated that 4 in 10 people are co-infected with HIV and *M* tuberculosis [22].

HIV alters the clinical presentation of tuberculosis, with an increased proportion of cases having extrapulmonary or disseminated disease, an effect that becomes more pronounced as HIV disease advances [23]. Pulmonary tuberculosis remains the commonest presentation, although the proportion is lower than for HIV-negative patients and the diagnosis may be delayed because the radiologic findings are often atypical [24]. In addition, in a study of HIV patients, sputum smears were positive in 40% to 76% of patients in whom the clinical suspicion of tuberculosis was high. The proportion of cases with smear-negative pulmonary tuberculosis ranged from 24% to 61% [25]. Tuberculous lymphadenitis is a more common finding in HIV-positive patients with FUO. Clinically, this can be difficult to diagnose because only abdominal lymph nodes may be involved and fever is often the sole feature of the disease. Abdominal CT and lymph node biopsy are frequently indicated, allowing for microscopic examination (which may show caseation or granuloma); staining for acid-fast bacilli; and cytologic examination and culture [26].
Blood culture is an extremely useful tool in the diagnosis of tuberculosis in HIV-positive persons, especially those with disseminated infection. Tissue nucleic acid amplification by polymerase chain reaction (PCR) should also be performed, especially in those with less than 200 CD4⁺/mm³ where sputum smears are frequently negative and there is clinical suspicion of an atypical mycobacterial infection [27]. In resource-limited settings, sputum smear and sputum culture remain the gold standard [28].

Disseminated MAC is the leading cause of HIV-associated FUO in northern Europe and the United States (31% of cases in the study by Armstrong and coworkers [11]), highlighting that the relative frequencies of individual infectious diseases accounting for FUO in HIV varies markedly depending on local prevalences. A single positive blood culture is considered evidence for disseminated MAC infection and mycobacteria recovered from other normally sterile body tissue sites including bone marrow, liver, lymph nodes, cerebral spinal fluid, or brain tissue should also be interpreted as indicative of disseminated disease. The yield of bone marrow aspiration for cultures is high in this setting and should be performed in cases of negative blood cultures [29].

Pneumocystis jiroveci pneumonia

*Pneumocystis jiroveci* pneumonia accounts for between 5% and 13% of cases of FUO in HIV, depending on regional variations in its prevalence. In patients with very low CD4⁺ counts, *P jiroveci* pneumonia often presents as prolonged fever before the onset of specific respiratory symptoms [14], whereas those with a relatively preserved CD4⁺ repertoire generally experience early shortness of breath [30]. Fever with a paucity of respiratory symptoms is characteristic of *P jiroveci* pneumonia as a cause of FUO in the late stages of HIV-AIDS. Diagnosis relies on demonstrating *P jiroveci* in induced sputum, bronchoalveolar lavage fluid, or in some cases transbronchial or open lung biopsy tissue [4,31]. In the era of HAART and antimicrobial prophylaxis, the mortality rate of *P jiroveci* pneumonia remains high (25%), whereas mortality in those not receiving antiretroviral therapy is 63% [32].

Cytomegalovirus infection

Cytomegalovirus (CMV) accounts for 5% of cases of prolonged, undifferentiated fever in HIV patients [4]. CMV is the most common HIV-associated viral opportunistic infection, typically manifesting when latent virus reactivates in patients with CD4⁺ counts less than 100/mm³. Patients may be asymptomatic, have nonspecific constitutional symptoms including isolated fever, or display localized end-organ disease [33]. Chorioretinitis remains the most common initial presentation, reported to occur in 30% of AIDS patients during the course of their illness [34]; other presentations that should alert physicians to the possible diagnosis of CMV infection, even
if the features are subtle, include hepatitis, enterocolitis, meningitis, radiculitis, myelitis, encephalitis, and pneumonia.

A variety of laboratory techniques are available for the rapid and reliable diagnosis of CMV infection including blood culture, detection of pp65 antigenemia, and PCR. Detection of CMV DNA in plasma [35] or whole blood [36] at the time of initial diagnosis of retinitis has been shown to be associated with a higher risk of mortality than a high HIV viral load. Similarly, asymptomatic patients with CMV DNA detectable in plasma at the initiation of HAART therapy had a significantly increased risk of developing subsequent CMV end-organ disease [37]. Furthermore, plasma CMV viremia is a stronger predictor of CMV disease and death than CD4-cell count or plasma HIV RNA concentration [38].

In HIV-infected patients with FUO and CMV viremia, it may be difficult to differentiate whether fever is caused by CMV reactivation. The decision to treat a patient for CMV solely on the basis of a positive plasma PCR result implies unnecessarily treating every third to fourth HIV-infected patient with CMV viremia. Therapy with antiviral drugs is associated with severe side effects and toxicity, such as myelosuppression, which may be particularly detrimental in patients with advanced HIV-infection. Consequently, isolated CMV viremia should only be treated after other causes have been carefully eliminated [39].

**Endemic mycoses**

Disseminated histoplasmosis caused by *Histoplasma capsulatum* var. *capsulatum* accounts for 7% of cases of HIV FUO in the United States, but very few cases have been documented in Europe [11]. Histoplasmosis is the first AIDS-defining event in 60% of cases in the United States [40]. The clinical symptoms (fever, malaise, weight loss) are nonspecific and common in HIV patients [41] and often clinically indistinguishable from that of disseminated MAC infection. Histoplasmosis should be considered in HIV-infected individuals with any unexplained febrile illness in endemic areas and in those with a previous history of travel to an endemic area, however long ago [42]. Markedly elevated lactate dehydrogenase levels may provide a clue to the diagnosis [43] but the highest yield is culture of blood or bone marrow, and bone marrow biopsy often allows rapid identification before culture or serologic results are available. In a series of 36 adult patients with AIDS and disseminated histoplasmosis, examination of bone marrow aspirates or biopsies resulted in rapid identification in one third of infected patients and also identified infections in some whose cultures were negative [44]. Blood culture remains a method limited by slow growth (2–4 weeks) [45] and serologic testing often lacks sensitivity in immunocompromised hosts. Detection of circulating *H capsulatum* polysaccharide antigen in urine and serum is available, but has false-positive rates in cases of other endemic mycoses caused by dimorphic fungi. PCR assay for histoplasmosis is not
Currently commercially available for routine use but is being investigated as a rapid method of identification.

Other endemic mycoses, such as coccidioidomycosis, may present as FUO in HIV-infected patients, particularly when the CD4\(^+\) cell count is below 250/mm\(^3\). A multivariate analysis identified black race and a history of oropharyngeal or esophageal candidiasis to be associated with an increased risk of coccidioidomycosis, and HIV protease inhibitor or azole therapy was associated with a reduced risk [46]. There are multiple manifestations of coccidioidomycosis in HIV infection including symptoms similar to those of pneumocystosis with dyspnea, fever, and night sweats, radiologically manifesting as diffuse reticulonodular pneumonia or focal primary pneumonia. Disseminated coccidioidomycosis, defined as disease that has spread beyond the thoracic cavity [47], is also common in HIV and some patients present with prolonged fever, weight loss, and no clear organ involvement [48]. Diagnosis is based on serologic analysis, culture, and histopathologic identification [49].

**Visceral leishmaniasis**

This opportunistic infection accounts for fewer than 5% of cases of HIV-FUO, although the prevalence of visceral leishmaniasis in HIV is increasing in developing countries. As the AIDS pandemic spreads to rural regions and leishmaniasis becomes more common in suburban areas, there is an ever-greater degree of overlap between the geographic distributions of the two diseases and, as a result, increasing rates of leishmaniasis-HIV coinfection. Such cases have been reported in 35 countries around the world, most in southwest Europe with a total of 1911 cases detected in Spain, France, Italy, and Portugal. The incidence is expected to continue to rise in eastern Africa and fall in southwest Europe, where increasing numbers have access to HAART. At diagnosis most patients with visceral leishmaniasis-HIV coinfection have fewer than 200 CD4\(^+\) cells and 50% meet AIDS-defining criteria. Fever, pancytopenia, and hepatosplenomegaly are found in 75% of cases. Only 40% to 50% of those coinfected have positive antileishmania antibodies [50] making diagnosis difficult, and antileishmania antibodies in HIV-positive patients are indeed 50 times lower than in HIV-negative patients [51], resulting in a number of false-negative results. The direct examination of amastigotes in spleen and bone marrow aspirates is the investigation of choice. Amastigotes appear in the peripheral blood in 50% of cases, with improved sensitivity using Novy-McNeal-Nicolle culture media [52]. Detection of *Leishmania* antigens by urine Western blot is currently being investigated, as are rk39 strips with a sensitivity and specificity close to 95% [53]. PCR on blood and tissue samples is increasingly used in clinical practice, and nested PCR assays have a sensitivity of 95% in peripheral blood and 100% in bone marrow [54].
Other infectious agents

Cryptococcosis and aspergillosis have both been implicated in FUO-HIV [55]. Although cryptococcosis may present as isolated FUO, concomitant meningoencephalitis is frequent (83%). Fungemia is seen in 40% of these cases, whereas urine culture is positive in 25% [56]. Mortality rate remains high despite HAART. A series demonstrated that mortality per 100 person-years was 63.8 in the pre-HAART era and 15.3 since the introduction of HAART, although early mortality did not differ between the two periods [57]. Although rare, aspergillosis is a serious complication in the advanced stage of AIDS (CD4+ <50/mm³). The diagnosis should be considered in those patients presenting with a new pulmonary cavity on chest radiograph [58] but can present as FUO.

In Asia, *Penicillium marneffei* is an important cause of FUO in HIV patients and may present as an emergent opportunistic infection in HIV-positive travelers to endemic regions [59]. Clinical signs include fever (99%); anemia (78%); weight loss (76%); generalized lymphadenopathy (58%); and hepatomegaly (51%). Skin lesions, most commonly papules with central necrotic umbilication, are seen in only 70% of HIV patients with FUO caused by disseminated *P marneffei* infection [60]. Diagnosis is by demonstration of the organism in blood cultures, antigen detection, or serologic analysis. HIV-positive patients tend to have lower serum antibody levels as a result of underlying immune defects. Their serum antigen levels are generally markedly higher, however, presumably because of a higher fungal load secondary to immune defects [61].

Toxoplasmosis has been demonstrated as a cause of HIV-associated FUO [55]. Isolated fever has been observed in severely immunocompromised HIV patients with extracerebral toxoplasmosis receiving trimethoprim-sulfamethoxazole as primary prophylaxis. PCR was positive for *Toxoplasma gondii* and fever resolved with high-dose toxoplasmosis treatment [62].

Physicians should maintain a high index of suspicion for *Bartonella* infection in HIV because recurrent fever occurs in 86% of cases. Recent data indicate that its prevalence among HIV-infected individuals may be much greater than previously reported [63]. The associated cutaneous lesions of bacillary angiomatosis are rarely present in the context of HIV infection [64]. Diagnosis is achieved through PCR or blood culture, and bartonellosis is usually easily treatable even in immunocompromised patients with late-stage HIV disease.

Infective endocarditis may present as FUO in the context of HIV and must be considered, especially in intravenous drug users. Small numbers of case reports implicate other infective agents in FUO of HIV-infected patients: nocardiasis in 2% of one series [8], *Rhodococcus equi* found in splenic microabscesses [13], babesiosis [65], and neurosyphilis [8]. The spectrum of infectious agents involved in HIV-associated FUO is wide, varies markedly
from that of the normal host, and reflects the geographic distribution of pathogens.

**Neoplasia**

Malignancies are a common and well-described cause of classic FUO in immunocompetent patients. In sharp contrast, malignancies represent only about 8% of cases of FUO in HIV. Only lymphomas, especially non-Hodgkin’s lymphoma, are highly represented, with incidences of 4% to 7% in case series [7,8,11,44,66]. Although most studies note a significant decrease in the global incidence of AIDS-related lymphoma in the HAART era, recent studies have found a threefold higher risk of Hodgkin’s disease in HIV-infected persons treated with HAART compared with those not treated [67]. In addition, the incidence of non-Hodgkin’s lymphoma has decreased less than other AIDS-defining illnesses and aggressive B-cell lymphoma has emerged as a common AIDS-defining illness [68]. Bone marrow involvement is frequently found in AIDS-related lymphoproliferative diseases (46%), and bone marrow biopsy may be helpful diagnostically [69].

FUO caused primary by central nervous system lymphoma and Kaposi’s sarcoma is less commonly encountered. Cases of prolonged fever associated with disseminated visceral Kaposi’s sarcoma account for 1% of cases [4], although Kaposi’s sarcoma with fever may be associated with Castleman disease. The incidence of Kaposi’s sarcoma has also decreased in the era of HAART [70]. Other cancers, such as primary lung and liver cancer, are increasingly found among HIV-AIDS patients [69] and may present as FUO, even in those receiving HAART [71].

**Drug fever**

Drug fever is an important consideration for FUO-HIV because drug allergy in HIV-positive individuals remains a major problem. The frequency of drug hypersensitivity in HIV-infected patients ranges from 3% to 20% and drug-related rashes have been estimated to be 100 times more common in HIV-positive patients than in the general population. The typical reaction of maculopapular pruritic rash, with or without fever, accounts for 17% of all adverse drug reactions and isolated fever is responsible for 1.7% [9]. Intake of multiple drugs including antiretrovirals and prophylactic-curative anti-infective therapy, in conjunction with high dosing regimens, changes in drug metabolism and interactions, immune hyperactivation, and oxidative stress, all in the context of advanced HIV disease, are risk factors for adverse reactions [70]. Hypereosinophilia is a clue to a drug hypersensitivity reaction but the diagnosis is established by withdrawal of the most likely offending drug, with most patients responding in 24 to 48 hours [72].

The drugs involved in hypersensitivity reactions have changed over the years. In the 1980s the commonest drugs responsible were the antimicrobials
used for prophylaxis of opportunistic infections, commonly trimethoprim-sulfamethoxazole, isoniazid, rifampicin, pyrazinamide, β-lactam antibiotics, sulphonamides, and dapsone. The rate of adverse drug reactions to trimethoprim-sulfamethoxazole was reported at 25% to 50%, with hypersensitivity reactions occurring in 30% of HIV-infected patients at prophylactic doses and in 50% at full therapeutic treatment doses (versus 1%–3% in HIV-negative patients) [73]. With the advent of HAART, adverse reactions to the antiretrovirals themselves have become increasingly important. A number of antiretroviral agents can cause hypersensitivity reactions but few are associated with fever more commonly than rash.

Abacavir, a nucleoside reverse transcriptase inhibitor, has been associated with severe hypersensitivity reactions in 3% to 5% of patients [72]. The reaction generally occurs after 9 days of treatment and is characterized by fever (80% of cases) and systemic symptoms with a rash occurring later in some patients. Such cases require termination of the drug. Rechallenge, which can be rapidly fatal, should not be attempted. Zidovudine-induced prolonged fever has also been documented [74] as has fever with nevirapine (15%) and amprenavir (7%) and anecdotally with virtually all antiretroviral drugs, but in most cases with an associated rash making them less likely etiologic agents in sole FUO. Enfuvirtide, which is administered subcutaneously, is generally responsible for local cutaneous reactions at the site of injection but can also provoke systemic symptoms, such as fever. The Swiss HIV Cohort Study found the use of combination antiretroviral treatment with two protease inhibitors and no non nucleoside reverse transcriptase inhibitors to be associated with greater risk of fever (and diarrhea) than alternative antiretroviral combinations [75].

**HIV**

Genne and colleagues [14] reported HIV itself as the cause of FUO in 27% of their series, a result not in keeping with the results of cohort studies. Primary HIV infection is associated with a nonspecific mononucleosis-like syndrome characterized by fever, rash, and lymphadenopathy in 40% to 70% of patients. The symptoms of primary HIV infection generally resolve spontaneously within 2 weeks, however, making it rarely the exclusive cause of the FUO. In HIV-infected patients presenting with FUO as their initial clinical manifestation of the HIV virus, coexisting opportunistic infection or malignancy are generally reported as responsible for the pyrexia [7,8,14].

**Immune reconstitution inflammatory syndrome**

In the initial period of HAART therapy, immune reconstitution may be complicated by adverse clinical phenomena (immune reconstitution inflammatory syndrome [IRIS]) where either previously latent infections are unmasked or pre-existing opportunistic infections apparently deteriorate.
This is seen in around 25% to 35% of HIV-positive patients. Most cases occur within the first 60 days of initiating treatment but the onset of IRIS may be seen for up to 2 years post-HAART initiation, predominantly in patients with low pre-HAART CD4+ cell counts. Fever is a common finding and cases of FUO attributed to IRIS have been reported [5]. IRIS is often associated with more specific, infection-associated signs, however, such as respiratory symptoms or inflammatory adenopathies in tuberculosis or raised intracranial pressure in cryptococcosis [51], focusing the diagnosis. Various infectious agents have been reported in the literature in association with IRIS, and Box 1 summarizes the pathogens. Mycobacteria are frequently implicated, accounting for around 30% to 40% of reported cases of IRIS. Shelburne and colleagues [76] described patients with prolonged fever in the context of IRIS associated with both underlying MAC infection and M tuberculosis. A further report presented a case of prolonged fever caused by a lymphoid interstitial pneumonitis during early IRIS after HAART initiation [77]. In addition, sarcoidosis has been reported as a cause of FUO after the onset of the HAART [78]. Treatment with interleukin-2 or interferon-α may be a risk factor for its development.

Miscellaneous causes

In smaller numbers of cases, HIV-associated FUO is caused by other noninfectious pathologies. Multicentric Castleman disease is a polyclonal lymphoplasmaacytic and vascular proliferation prominent in lymphoid tissues and associated with constitutional symptoms and prominent fever. Cases have presented as FUO in HIV [11]. There is a prominent role for human herpes virus-8 and cytokine dysregulation in this disorder and it remains a challenging clinical problem in the HIV-infected population. Cases of FUO-HIV caused by systemic lupus erythematosus and Reiter’s

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syndrome have been reported [79]. In contrast with classic FUO, however, autoimmune and inflammatory conditions constitute a small percentage of cases. Single cases of FUO-HIV caused by neuralgic amyotrophy [7] and subacute thyroiditis [80] exist in the literature, as do a limited number of episodes of factitious fever presenting as FUO in HIV [9].

Multiple etiologies or no cause found

A cause of FUO in HIV is elucidated in around 80% of cases [31]. Immunocompromised individuals are vulnerable to a wide variety of infectious agents and multiple etiologies are responsible for between 8% and 19% of individual cases of FUO, a situation not commonly seen in classical FUO. One series found 12.5% of patients with a diagnosis of two etiologic processes and 3.3% with three. Should fever persist despite adequate treatment for a diagnosed entity, further studies should be performed to rule out coexisting conditions.

The cause of HIV-associated FUO remains unidentified in 6% to 14% of reported series, a proportion apparently unaltered in the era of HAART. This is more frequently seen in the very latest stages of HIV infection, where an exhaustive investigation is more complicated given the risks of invasive diagnostic procedures. In the absence of a diagnosis, nonsteroidal anti-inflammatory drugs or corticosteroids can be used as antipyretic agents and empirical antimycobacterial therapy should be initiated.

Evaluation of the patient with fever of unknown origin in the context of HIV

Physicians confronted with an HIV-infected patient with FUO should take into account the relative frequencies of causative agents as previously discussed and the geographic setting of the patient, including any history of travel. Initially, a detailed medical history should be obtained and a thorough physical examination performed including ophthalmologic examination for CMV retinitis, which may suggest a likely etiology. Review the patient’s previous isolates because some microorganisms are chronic colonizers of the respiratory and digestive tracts. Attention should also be directed to the patient’s medications. If the fever started in the 10 to 14 days following a change or addition of a drug, drug fever must be considered, especially when accompanied by a rash or gastrointestinal symptoms.

Noninvasive investigations should follow. Appropriate blood cultures remain the most important investigation in determining the cause of FUO in HIV patients, useful in diagnosing disseminated tuberculosis; disseminated MAC [81]; disseminated histoplasmosis; and a variety of bacterial and fungal pathogens including Cryptococcus neoformans, Bartonella sp, R equi, and P marneffei [13]. Blood cultures should ideally be incubated in DuPont Isolator (Wampole Laboratories, Cranbury, Jew Jersey) or Bectec (Becton
Dickinson Diagnostic Instrument Systems, Sparks, Maryland) medium and held for a sufficient time period of time to demonstrate pathogens. Blood should be stained for acid-fast bacilli and fungi. Examination of the blood smear without culture may demonstrate such organisms as *Leishmania infantum* and *H capsulatum* in Europe or *Leishmania donovani* in India [82]. The latex agglutination test for *Cryptococcus* detection has high sensitivity and specificity for disseminated cryptococcosis including meningitis [56]. CMV can be detected by pp65 antigenemia or PCR on a blood sample. Antibody detection is of little value in diagnosing FUO in patients with less than 200 CD4\(^+\) lymphocytes/mm\(^3\). The test for anti-*Toxoplasma* antibodies has only a high negative predictive value, although in severely immunocompromised hosts, a negative test does not exclude active toxoplasmosis [37].

Other noninvasive methods include analysis of sputum for *P jiroveci* and *M tuberculosis*. Urine and stool culture are of little value unless there are relevant symptoms. Abdominal and thoracic CT should be performed early because they have a high diagnostic yield and may assist in the identification of two of the most common causes of FUO: mycobacterial infection and lymphoproliferative disorders. Cerebral CT may be useful in anti-*Toxoplasma* antibody carriers with a low CD4\(^+\) cell count.

**Nuclear imaging**

Fluorodeoxyglucose positron emission tomography scanning is commonly used in the investigation of FUO in immunocompetent hosts and has an emerging role as a rapid whole-body assessment in FUO in HIV, although availability and cost limits its widespread use. O’Doherty and colleagues [83] first reported its use in FUO in HIV in 1997, where 29 patients presented with moderate or high uptake of fluorodeoxyglucose, the scans successfully localizing tumor in those with non-Hodgkin’s lymphoma in soft tissue, nodal, and bone sites. Positron emission tomography allows accurate and rapid localization of malignant and infectious diseases in patients enabling biopsy of specific sites to be performed. In some cases, however, it may be difficult to distinguish malignancy from inflammatory causes (Fig. 1). The use of \(^{67}\)Ga-citrate has not been shown to be superior to fluorodeoxyglucose positron emission tomography in the only available study to date [84].

**Bone marrow examination**

Bone marrow aspiration or biopsy and culture are a high-yield procedure in HIV-positive patients with FUO [85]. Benito and colleagues [86] investigated such a group, reporting specific diagnoses by means of culture and histopathologic examination in 38% of those biopsied. The diagnostic yield reported in other studies ranges from 25% to 34% [87,88]. Diagnoses elicited by bone marrow biopsy include extranodal non-Hodgkin’s
lymphoma; mycobacterial infection (although blood culture is more sensitive in identifying MAC infection); drug-induced changes; and Castleman disease.

Liver biopsy

The overall diagnostic yield of liver biopsy in HIV-associated FUO is 45% [4], increasing to 80% in disseminated mycobacterial disease [89]. In a study performed pre-HAART, 26.8% of HIV patients with FUO underwent percutaneous liver biopsy as part of the diagnostic work-up and the biopsy was diagnostic in 43% of cases and contributory in a further 22.4% [90]. The presence of hepatosplenomegaly and lone splenomegaly has a high predictive value of a positive liver biopsy, and raised serum alkaline phosphatase levels are a clinical marker of the usefulness of liver biopsy in cases of tuberculosis [91]. Liver biopsy should be performed in the context of a raised alkaline phosphatase level or hepatosplenomegaly after exhaustive, nonconfirmatory, noninvasive investigations [92].

Fig. 1. Immune reconstitution inflammatory syndrome demonstrated on fluorodeoxyglucose positron emission tomography scanning in a 39-year-old HIV-positive man with tuberculosis 1 month after initiating antituberculous therapy. Lymphadenitis with fluorodeoxyglucose uptake in multiple areas.
Biopsy of skin lesions or peripheral lymphadenopathy

If skin lesions or peripheral lymphadenopathy are new or altering in size or number, biopsies should be obtained. Lymph node biopsy has a high diagnostic yield and may aid in the detection of lymphomas, disseminated mycobacterial disease, and toxoplasmosis. Skin lesions are more often a clue to drug hypersensitivity reactions or disseminated infection as opposed to localized infection [31].

Other investigations

Transthoracic echocardiography (sensitivity 63%, specificity 98%) and transesophageal echocardiography (sensitivity 100%, specificity 98%) may allow early detection of valvular vegetations in the context of infective endocarditis [93]. These tests should be high priority in HIV-infected intravenous drug users where FUO may be the sole clinical feature of infective endocarditis [94].
Diagnostic approach

Diagnosing FUO in HIV-infected patients requires attention to detail, and although no formal protocol exists [4,10], a systematic approach using all available investigative methods is advised. Fig. 2 represents a proposed algorithm for the diagnostic work-up of HIV-associated FUO. Empirical treatments are best avoided but therapeutic attempts with antibiotics, antimycobacterial agents, or corticosteroids may be indicated in cases of clinical deterioration or when both clinical suspicion is high and the risks derived from a delay in the initiation of therapy are significant. Tuberculosis remains a paradigm of this situation [95]. Stopping empirically introduced antimicrobial agents is advised if cultures remain negative and if clinical states fail to improve.

Summary

FUO in HIV-AIDS patients remains a challenge. HAART has contributed to a decrease in its incidence but has not altered the spectrum of causes. It is a common cause of admission to hospitals and is associated with substantial cost and significant mortality. In most cases FUO in the context of HIV is a result of occult opportunistic infection and physicians should take into consideration differing geographic prevalences of infectious pathogens. If no infectious cause can be demonstrated, AIDS-related lymphoproliferative diseases and drug fever should be considered along with a number of less common etiologies. The diagnostic work-up is initially directed toward infection, which remains the single leading etiology. The single most important early investigation is blood culture. Bone marrow examination, liver biopsy, and newer nuclear imaging techniques are useful further diagnostic modalities. An algorithm for the diagnostic approach and management of patients with HIV-associated FUO is presented.

References


