

## Original article

## PATIENTS WITH HIV INFECTION AND FEVER: A DIAGNOSTIC APPROACH

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### ABSTRACT:

Fever is a common sign among patients with HIV infection and frequently leads to a medical consultation. It is generally caused by infections. The type of infection depends on the stage of the disease. Opportunistic infections occur only in the presence of severe immunodeficiency. A systematic approach will identify most causes of fever. Since the incidence of opportunistic infections has dramatically decreased with the use of highly active antiretroviral treatments, other causes of fever including immune restoration disease, neoplasm and drug-fever should be considered.

### 1. Introduction :

Fever is common in the course of HIV infection. Before the use of highly active antiretroviral therapy (HAART), fever in HIV patients was often caused by opportunistic infections (OIs). Since the introduction of

HAART, the incidence of AIDS defining OIs decreased by 50 to 80% [1]. Other conditions such as hypersensitivity reactions, immune restoration disease and neoplasms should therefore increasingly be considered in the diagnostic work up of fever in patients with HIV infection. The purpose of this article is to review the diagnostic approach to fever in patients with HIV infection. Important factors to be considered in the evaluation of fever in people with HIV infection are shown in table 1.

**Table 1: factors to be considered in the evaluation of fever among patients with HIV infection:**

- Stage of disease and degree of immunodeficiency
- Medical history, physical examination and paraclinical investigations
- Fever in specific patient groups (IV drug users, travellers and migrants)
- Non-infectious causes of fever
- Fever of Unknown Origin

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### 2. Disease stage and pattern of opportunistic infections

#### A. Primary infection

Probably 40 to 70% of all new HIV infections are symptomatic [2]. Infectious mononucleosis-like symptoms usually develop two to four weeks after infection and last about two weeks. Fever is present in 50% [3] to 90% [4] of cases. Other frequent symptoms/signs include a maculo-papular rash, enlarged lymph nodes and a pharyngitis. Almost 40% of the patients are unable to work and need hospital admission [3]. The diagnosis of

acute HIV infection is a real challenge since conventional HIV antibody tests are often negative. A more sensitive test is the detection of plasma viral RNA but it can yield false positive results [4]. This test becomes on average positive two weeks after infection and three weeks earlier than the conventional antibody assays [5]. If for some reason (price, technical constraints) the determination of plasma HIV RNA is impossible, the detection of p24 antigen is indicated. The sensitivity of this test is 88.7% [4]. A recurrence of an acute HIV syndrome a few weeks after discontinuation of HAART has been described [6].

**B. *Early stage disease, no immunodeficiency (CD4+ lymphocyte count > 500/μl)***

The development of OIs at this stage is unlikely, with the exception of tuberculosis (TB). Fever should be evaluated as in immunocompetent hosts.

**C. *Mild to moderate immunodeficiency (CD4+ lymphocyte count between 200/μl and 500/μl)***

Patients may develop infections with pathogens that also cause disease in immunocompetent hosts but often these infections will be more severe or recurrent, e.g. TB, *Herpes zoster* infection, *Salmonella* sepsis and pneumonia (especially caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*) often associated with bacteraemia [7].

**D. *Severe immunodeficiency (CD4+ lymphocyte count < 200/μl)***

Patients are at risk of developing AIDS defining events (table 2).

*Pneumocystis carinii* classically causes a subacute pneumonia (PCP) frequently complicated by severe hypoxia. Constitutional symptoms and low-grade fever

**Table 2 : Correlation between CD4+ lymphocyte count and opportunistic pathogens causing fever:**

CD4+ COUNT	Pathogen	Clinical picture
>500/μl	HIV	acute seroconversion
<500/μl	<i>Haemophilus influenzae</i> <i>Herpes zoster</i> Virus <i>Mycobacterium tuberculosis</i> <i>Streptococcus pneumoniae</i>	Pneumonia, sinusitis Shingles-varicella Pulmonary tuberculosis Pneumonia/bacteraemia
<200/μl	<i>Candida</i> sp. <i>Cryptococcus neoformans</i> <i>Herpes simplex</i> Virus <i>Herpes zoster</i> Virus <i>Histoplasma capsulatum</i> <i>Mycobacterium tuberculosis</i> <i>Pneumocystis carinii</i> <i>Salmonella non typhi</i> <i>Toxoplasma gondii</i> ?	Oesophagitis Cryptococcosis, meningitis Muco-cutaneous disease/encephalitis Disseminated infection Histoplasmosis Miliary and extra-pulmonary tuberculosis Pneumonia Bacteraemia Toxoplasmosis, intra-cerebral abscess Non-Hodgkin lymphoma
<50/μl	Cytomegalovirus <i>JC</i> Virus <i>Mycobacterium avium/intracellulare</i>	Disseminated infection Progressive Multifocal Leucoencephalopathy Disseminated infection

are sometimes predominant in the clinical picture [8]. The incidence of PCP decreased considerably since the use of HAART and primary and secondary PCP prophylaxis.

Tuberculosis often with an atypical clinical presentation (disseminated and/or extrapulmonary form) also occurs at this stage of the disease.

In Europe and the U.S, *Mycobacterium avium* complex (MAC) is the most frequent cause of persistent fever among patients whose CD4+ lymphocyte count drops below 50/ $\mu$ l. In most patients there is multi-organ involvement (bone marrow, lymph nodes, gut, liver) [9].

Cytomegalovirus (CMV) is another important complication in late stage disease. The eye (retinitis) and the gastro-intestinal tract (oesophagitis, colitis and hepatitis) are most commonly involved. [10].

Serious bacterial infections with common pathogens are also frequent in patients with severe immunodeficiency. Bacterial pneumonia is in almost half of the cases clinically and radiologically [11] indistinguishable from PCP [12]. Fever may also be caused by uncommon bacteria such as *Nocardia* [13], *Rhodococcus equi* [14] and *Bartonella henselae* [15].

### 3. Evaluation of fever among patients with HIV infection

The diagnostic approach of fever in people with HIV infection is summarized in table 3. The **medical history** should focus on associated symptoms (e.g. rash, cough, dysphagia, headache and diarrhoea), previous OIs, the latest CD4+ lymphocyte count, the current treatments (HAART and prophylactic drugs) and adherence. Patients should also be questioned about unprotected sex in the last three months. It exposes them to other sexually transmitted diseases such as hepatitis B (which can cause fever two to three months after exposure). Secondary syphilis also presents frequently with constitutional symptoms including low-grade fever (70% of the patients) [16]. HIV broadens the clinical spectrum of syphilis, co-infected patients may therefore present with atypical forms of syphilis [16]. A resurgence of syphilis has recently been documented among homosexual males in Europe and the US [17].

A **physical examination** will confirm the presence of fever. Careful skin and mouth inspection may reveal evocative lesions (shingles, candidiasis, Kaposi's sarcoma, cryptococcosis, abscesses or a drug-associated rash). The palpation of lymph node regions may identify enlarged lymph nodes potentially caused by extra-

**Table 3: Diagnostic work up for initial evaluation of fever among patients with HIV infection:**

- Anamnesis and system review
  - Associated symptoms
  - Last CD4+ lymphocyte count
  - Current treatment and adherence
  - Recent history of drug intake, travel or unprotected sexual contact.
- Physical examination:
  - Axillary temperature
  - Skin lesions and lymph nodes palpation
  - Chest examination
  - Abdominal examination
  - Neurological examination.
  - Genital and rectal examination.
- Laboratory tests:
  - Complete blood count with differential counts
  - Blood chemistry (transaminases, alkaline phosphatase, LDH)
  - Urinalysis & culture
- Additional tests:
  - Chest X-ray
  - Abdominal ultrasound
  - Fundoscopy
  - Blood cultures.
  - Stool examination
  - Lumbar puncture
  - Syphilis and Toxoplasma serology
  - CT scan of the brain

pulmonary TB, atypical mycobacteriosis, hypersensitivity reactions or non-Hodgkin lymphomas (NHL). A thorough chest examination may identify a pulmonary infection (bronchopneumonia, pneumonia) and a cardiac murmur. PCP may present with a normal chest auscultation. Hepatosplenomegaly suggests a disseminated mycobacterial infection or a lymphoma. Focal neurological deficits are generally the consequence of intracerebral lesions caused by toxoplasmosis, lymphoma, tuberculosis and brain abscesses. Some central nervous system infections can be pauci-symptomatic and only present with fever and headache (e.g. cryptococcal meningitis). Finally, the diagnostic work up should include a genito-rectal examination to detect genital or rectal ulcers, urethral discharge, anal abscess or prostatitis.

The following **laboratory tests** may be useful: a complete blood count with differential count, CD4+

lymphocyte count, transaminases, lactate dehydrogenase (often elevated in PCP, TB, histoplasmosis, toxoplasmosis and NHL [18]), alkaline phosphatase (high in disseminated mycobacterial disease [19]) and urine analysis and culture.

In the presence of localized signs or symptoms *other investigations* may be required:

- A chest X-ray to look for pulmonary infiltrates, mediastinal lymph nodes and pleuro-pericardial effusions among patients with cough or dyspnoea. Chest X-rays of patients with pulmonary TB and advanced immunodeficiency are however frequently atypical [20] and may remain normal in 10 to 30% of pulmonary TB [21] and PCP [22]. Patients with a strong suspicion of lung disease and a negative or inconclusive chest X-ray should undergo a bronchoscopy and a bronchoalveolar lavage for the detection of *P. carinii*, mycobacteria and fungi [23].
- An abdominal ultrasound [24] to look for ascites, organomegaly, pancreatitis, enlarged lymph nodes or intra-abdominal abscesses.
- A fundoscopy to detect CMV lesions [25], miliary tuberculosis and toxoplasmosis.
- Blood cultures, including cultures for mycobacteria which should be performed on special culture media (e.g. Löwenstein-Jensen medium) or using special techniques such as the radiometric system (Bactec®, Becton-Dickinson, USA) [26].
- A parasitological stool examination, a stool culture and a *Clostridium difficile* toxin assay on stools from in-patients with diarrhea. The most common enteric pathogens associated with fever in patients with HIV infection are *Salmonella*, *Shigella* and *Clostridium difficile*. Opportunistic pathogens like *Isospora*, *Microsporidium* and *Cryptosporidium* are usually not associated with fever.
- Syphilis (VDRL and TPHA) [27] and *Toxoplasma* (IgG antibodies) serology should be requested for all patients with central nervous system symptoms.
- A CT scan of the brain is indicated in the presence of focal neurological deficits or convulsions.
- A lumbar puncture should be performed in case of unexplained headache or neurologic symptoms. Microscopic examination of the cerebrospinal fluid (CSF) should include Gram stain, Ziehl-Neelsen stain, Indian ink, culture and determination of glucose and protein levels [28]. If available a PCR for *Herpes simplex* and CMV as well as cryptococcal antigen on CSF should be performed.

#### 4. Fever in specific patient groups

##### A. Intravenous drug users

Intravenous drug use is associated with a high risk of transmission of hepatitis B and C, two potential causes of fever in the acute phase of the infection. Infective endocarditis is the most frequent cause of bacteræmias (*Staphylococcus aureus*) among drug users [29]. Skin and soft tissue infections (thrombo-phlebitis, cellulitis, abscesses and necrotizing fasciitis) are also frequent in this population. The principal pathogens are *Staphylococcus aureus* and *Streptococcus* sp. In 2000, an outbreak of *Clostridium* sp. sepsis due to a contaminated batch of heroin has been described among Scottish drug users [30]. In Mediterranean countries visceral leishmaniasis is a frequent cause of fever in HIV-infected intravenous drug users [31].

##### B. Travellers/Migrants

The patient's country of origin and travel history should always be taken into account since the prevalence of pathogens varies widely from one region to another. For example *Penicillium marneffeii* and *Cryptococcus neoformans* are particularly frequent in South-East Asia [32], *Plasmodium* sp. in Africa [33], *Histoplasma capsulatum* in South-America [34] and *Leishmania* sp in the Mediterranean region .

#### 5. Other causes of fever

##### A. Immune restoration diseases

Patients starting HAART in late stage disease may develop fever as part of an inflammatory syndrome a few weeks after the initiation of the treatment. This has been explained by the restoration of a specific immunity against a sub-clinically pre-existing pathogen [35]. Recurrence of CMV retinitis [36], inflammatory mycobacterial adenopathies [37], hepatitis flares in chronic hepatitis C [38] and herpes infections [39] have been described.

##### B. Neoplasms

So far, HAART has not reduced the global incidence of NHL [40]. NHL is often present with fever and systemic symptoms. B symptoms also occasionally occur in patients suffering of Kaposi's sarcoma with visceral involvement [41]. Other proliferative diseases such as Castelman's disease have been associated with fever in HIV infected persons [42].

### C. Drug-induced fever

Fever is a possible side effect of many drugs. HIV infected patients, especially in late stage disease, are more likely to develop drug fever [43]. The rate of adverse drug reactions (rash and fever) to co-trimoxazole in HIV infected persons is reported to be as high as 25 to 50% [44]. Dapsone [45],  $\beta$ -lactams and anti-epileptics also frequently cause fever in HIV positive patients [46]. Patients on abacavir [47], nevirapine [48] or efavirenz [49] may develop a hypersensitivity syndrome often referred to as DRESS (drug rash, eosinophilia and systemic symptoms). It occurs usually 2 to 6 weeks after the introduction of the antiretroviral drug. Immunotherapy is an experimental therapeutic option for persons with HIV infection. Interleukin-2 may increase the CD4+ lymphocyte count but fever has been reported in 45 % of patients using this drug [50].

### 6. A particular case: fever of unknown origin (FUO)

FUO has been defined as fever higher than 38.3°C for more than three to four weeks for out-patients or as fever above 38.3°C without a diagnosis after three days of appropriate investigations for in-patients [51]. FUO in patients with HIV infection should be investigated differently than in immuno-competent hosts. Before the use of HAART, infection was the major cause of FUO in patients with HIV infection and multiple pathogens were commonly found [8]. The most common causes observed in a meta-analysis of 8 European series since 1992 [8] were *Mycobacterium tuberculosis* (37%), atypical mycobacteria (12%), *Leishmania* sp. (12%) and bacteræmia (7%). This should be handled with caution since most of these studies were retrospective. Moreover some geographical (80% of the patients came from Spain) and epidemiological characteristics (high prevalence of drug users) could be responsible for the overrepresentation of certain conditions such as *Leishmania* infections and tuberculosis. The incidence of FUO has been estimated at 8,3 cases per 100 patient-years in one prospective study before the HAART era [52]. Some "sanctuary organs" like the paranasal sinuses [53] or the prostate [54] are often forgotten infection sites in patients with HIV infection. Any drug susceptible of causing fever should be discontinued before starting any invasive diagnostic procedure. If a basic fever work up does not yield a diagnosis and depending on the clinical context, the following diagnostic procedures may be indicated: a thoraco-abdominal CT scan, a bone marrow

biopsy [55], a liver biopsy [56] or a Gallium-67 or Indium-111 labelled scan [57]. A liver biopsy has a diagnostic yield as high as 75% for mycobacterial disease, especially when the serum alkaline phosphatase level is high (> 2.5 times above normal range) [58]. The yield of bone marrow examination in patients with HIV infection ranges from 13 to 42% [59]. Biopsies from skin lesions and enlarged lymph nodes should be sent for histology and culture (bacterial, fungal, mycobacterial). According to the clinical picture, antigen and PCR detection tests for CMV, *Cryptococcus neoformans* and *Histoplasma capsulatum* may be helpful.

### 7. Conclusion

Fever is a common sign in the course of HIV infection. Before the HAART era, fever was often caused by an opportunistic agent such as mycobacteria, CMV and toxoplasma. Since the incidence of OIs decreased dramatically with the introduction of HAART, other causes of fever such as immune restoration disease, neoplasm and drug fever should increasingly be considered.

### RÉSUMÉ

La fièvre est un signe clinique commun chez les patients infectés par le VIH et elle est souvent une cause de consultation médicale. La fièvre est généralement causée par une infection dont le type dépend du stade de la maladie, les infections opportunistes ne survenant qu'à un stade avancé de la maladie. Une approche systématique permet d'identifier la majorité des cas de fièvre. Puisque l'incidence des infections opportunistes a considérablement diminué depuis l'introduction des traitements antirétroviraux combinés, d'autres causes de fièvre, telles que les syndromes de reconstitution immunitaire, les néoplasies et les fièvres médicamenteuses doivent donc être considérées.

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