Original Articles

Aetiology of prolonged fever in antiretroviral-naïve human immunodeficiency virus-infected adults

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ABSTRACT

Background. Prolonged fever is a common symptom among human immunodeficiency virus (HIV) infected individuals, and is usually due to a cause that is easily treatable. Limited data are available regarding the causes of fever in HIV-infected Indian patients. In this paper, we have profiled the causes of prolonged fever in a cohort of HIV-infected Indian patients and have developed suitable algorithms to assist in an early diagnosis.

Methods. From February 1997 to October 1998 (20 months), 100 HIV-infected patients (age >12 years) were evaluated for 100 episodes of prolonged fever (fever >100 °F for more than 2 weeks in outpatients and >3 days in inpatients). Patients with terminal acquired immunodeficiency syndrome (AIDS) were excluded. Patients were evaluated on the basis of the symptoms associated with prolonged fever and investigated according to pre-existing algorithms.

Results. Among such episodes of fever, infection was the major cause and included tuberculosis, especially the extra-pulmonary and disseminated forms (69%), cryptococcosis (10%) and *Pneumocystis carinii* pneumonia (7%). Other causes included bacterial pneumonia, amoebic liver abscess, disseminated histoplasmosis and cerebral toxoplasmosis. Patients were naïve for antiretroviral therapy and did not receive prophylaxis for opportunistic infections. The diagnostic yield of ultrasound of the abdomen (85%), fine-needle aspiration cytology of enlarged lymph nodes (75.6%) and bone marrow trephine biopsy (41.6%) were found to be high in our study.

Conclusions. Tuberculosis is the commonest cause of prolonged fever in HIV-infected adults in India. Non-infectious causes were not seen in this series. We have suggested an algorithmic approach for establishing the cause of fever in these patients. In situations where laboratory evaluation does not reveal a cause for prolonged fever, a therapeutic trial with anti-tuberculous therapy in selected patients is justified.

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INTRODUCTION

India has an estimated 3.97 million people living with human immunodeficiency virus (HIV) infection. Currently, India ranks second among countries whose young and adult population is infected with the virus.[1] HIV infection encompasses a clinical spectrum ranging from an acute seroconverting syndrome (1–14 days), an asymptomatic phase of a variable duration (5–10 years), and an advanced immunosuppressed phase (1–2 years), which ends in death in the absence of antiretroviral therapy (ART). Fevers of short (3–7 days), or long (>7 days) duration are common presenting symptoms in people living with HIV infection and acquired immune deficiency syndrome (AIDS) (PLWHA).[2]

It is critical to identify the causes of prolonged fever (>14 days), because the vast majority are due to an opportunistic infection (OI) that is easily treatable.[3–6] Agents causing prolonged fever such as *Cryptococcus* spp*., Pneumocystis carinii, Toxoplasma gondii*, etc. occur commonly when the CD4 cell count is <200/cmm. However, in those with CD4 cell counts between 200/cmm and 500/cmm, even relatively virulent pathogens such as *Mycobacterium tuberculosis* and *Salmonella* spp., which can cause prolonged fever in a normal individual, occur at an increased frequency. With CD4 counts >500/cmm, the same wide array of organisms that cause prolonged fever among normal individuals could be responsible. Hence, due to this uncertainty, diagnostic evaluation of prolonged fever in PLWHA can be exhaustive and difficult.

Currently, for ease in establishing the aetiology of prolonged undifferentiated fever among the adult population, the standard clinical approach is to categorize patients as 'classic'; noso-comial; neutropenic; and HIV-associated.[7] Such categorization improves the diagnostic approach by narrowing down the possible aetiology. Therefore, for the HIV-infected population, numerous workers at different medical centres, after profiling the cause of prolonged fever depending on the disease endemicity, stage of the disease based on the CD4 cell counts and status of prior OI prophylactic therapy, have suggested algorithms to assist clinicians. An evaluation based on CD4 cell counts does provide the best clue to the underlying aetiology. However, in countries such as India where ART is non-affordable, and the vast majority of medical centres lack laboratory facilities to determine the CD4 cell count, or perform invasive and specialized diagnostic tests, clinicians need an alternative approach. By systematically chronicling diseases causing prolonged fever in 100 HIV-infected antiretroviral-naïve patients, without utilizing CD4 cell counts, we derived data to suggest clinical algorithms based on localizing symptoms involving two major organ systems, and specific findings (both laboratory and clinical) that are simple and may be practical in resource-limited clinical settings.

PATIENTS AND METHODS

This prospective study was conducted during a 20-month period from 1 February 1997 to 31 October 1998, in a tertiary care referral medical centre (>1750 beds) located in south India (Tamil Nadu).

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The inclusion criteria were: patients above the age of 12 years who had previously tested positive for HIV antibody [initially reactive sera retested and confirmed by enzyme-linked immunosorbent assay (ELISA) test, or by Western blot] and presented with prolonged fever, i.e. temperature recordings >100 °F documented on at least two separate occasions over a period of 3 post-hospitalization days, or for >14 days, with at least 2 outpatient visits that recorded temperatures >100 °F. We excluded those with prolonged fever who were terminally ill with AIDS and whose survival during the period of fever evaluation was considered unlikely. Those patients in whom the fever was diagnosable with initial positive laboratory screening (complete blood counts, smear for malarial parasites, Widal test or a positive urine and blood culture within 48 hours) were also excluded. Only a single episode of fever that occurred among these 100 patients was included.

One hundred consecutive HIV-infected patients presenting with prolonged fever were evaluated and the outcomes followed up. Over 80% were inpatients (during this period over 510 HIV-infected patients had been hospitalized) and the rest were from the outpatient services of the three General Medicine units and Infectious Diseases clinic. Patients were assessed for duration of fever, duration of HIV seropositivity, mode of acquisition of HIV infection and prior therapy for this episode of fever. Patients were categorized into groups based on the major localizing symptoms or physical findings associated with their prolonged fever. Patients in group 1 included those with prolonged fever alone without any specific localizing symptoms; group 2 included those with prolonged fever and any one of the following respiratory symptoms or signs: cough, breathlessness, chest pain, wheezing or sputum production; and group 3 included those with prolonged fever and any one of the following neurological symptoms or signs: headache, altered sensorium, seizures or focal neurological deficits.

Patients underwent a detailed physical examination and were investigated to establish an aetiology as per the symptom-specific algorithms validated by the Johns Hopkins University (JHU) for similar groups.[8]

Investigations focused on the specific symptoms or signs of the major organ systems involved. Ultrasound scan of the abdomen, computerized tomography (CT) scan of the head, and invasive procedures [such as fibreoptic bronchoscopy, bone marrow aspiration and core biopsy (using a Jamshedi needle), lymph node excision biopsy/aspiration cytology and percutaneous needle (Tru-cut) biopsy of the liver] were done if the initial non-invasive diagnostic procedures yielded negative results. The tissue samples obtained from invasive procedures were microscopically examined after formalin fixation and appropriate staining (haematoxylin–eosin, periodic acid-Schiff, Ziehl–Neelsen). Microbiological evaluation included specimens stained with Ziehl–Neelsen and Gram stain of appropriate body fluids. Unfixed bone marrow and liver biopsy specimens were cultured for bacteria, mycobacteria and fungi by standard procedures.

The laboratory test or method that diagnosed the cause of fever was recorded. When multiple tests provided the diagnosis in an individual patient, the one that first proved the diagnosis was recorded. To arrive at the diagnosis, the JHU algorithms were followed as far as possible, but the final choice of investigations was left to the discretion of the attending physician. The study protocol was approved by the institutional review board.

The diagnostic yield of a test was calculated as the percentage of patients with a positive diagnosis against the total number of tests done.

The criteria used to define the disease status were as follows:

Tuberculosis (TB)
1. *Pulmonary TB:* Acid-fast bacilli (AFB) seen on the smear or *M. tuberculosis* grown in culture, in specimens obtained from pulmonary secretions (sputum, bronchoalveolar lavage, pleural fluid), or chest X-ray showing infiltrates (miliary or subsegmental), consolidation or pleural effusion. Sputum cultures for bacterial pathogens had to be negative in these patients.
2. *Extra-pulmonary TB*
   a. *Lymph nodal:* AFB or granulomas seen on smears of fine-needle aspirates (FNA) or on histopathological examination of excised lymph nodes in patients with response to conventional antitubercular therapy (ATT).
   b. *Peritoneal:* Exudative ascites (as defined by any one of the following: a serum and ascitic fluid albumin gradient <1.1; a ratio of ascitic fluid protein and serum protein >0.5); with or without ultrasound demonstration of loculated ascites, in patients with response to conventional ATT.
   c. *Meningeal:* Cerebrospinal fluid (CSF) pleocytosis (>5 white blood cells/cmm) with lymphocytic predominance (>85%), elevated protein (>40 mg/dl) and lowered glucose (<40 mg/dl) levels, in patients with response to ATT. AFB seen on CSF smears and growth of *M. tuberculosis* in culture were additional diagnostic features.
3. *Disseminated TB:* affectation of (i) two or more anatomically non-contiguous organ sites, or (ii) bone marrow alone [with demonstration of AFB in body fluid specimens/tissues, or granulomas (with or without caseous necrosis) on histopathological examination of tissue obtained from at least one affected site], or (iii) patients with affectation of two or more anatomically non-contiguous organ sites lacking histopathological or microbiological evidence of TB, but who on follow up improved clinically with regression of the lesions on ATT.

An affected organ site included any of the following (i) lymph nodal: marked peripheral lymphadenopathy; (ii) abdominal: palpable hepatomegaly, palpable splenomegaly, elevated alkaline phosphatase level (>125 U/L), ultrasonographic evidence of intra-abdominal lymphadenopathy, hypoechoic areas seen in either the liver or spleen, loculated ascites; (iii) lung: chest X-ray with either infiltrates or consolidation, mediastinal lymphadenopathy or pleural effusion; (iv) meninges: CSF analysis typical of meningeal TB (*see above* 2c); (v) pericardium: exudative form of pericardial effusion.

Pneumocystis carinii pneumonia (PCP)
Bilaterally diffuse interstitial infiltrates seen on chest X-ray with associated hypoxaemia (PaO_2 <90 mmHg) and sputum smears/cultures negative for aerobic bacteria or AFB. A direct fluorescent antibody (DFA) test positive for *P. carinii* antigen in specimens of induced sputum or bronchoalveolar lavage was an additional feature.

Cryptococcosis
1. *Meningeal:* CSF India ink smear showing *Cryptococcus* spp., or cryptococcal antigen in CSF or growth of the organism in culture.
2. *Disseminated cryptococcosis*: *Cryptococcus* spp. isolated from two different organ sites, or organism grown in blood culture alone.

Cerebral toxoplasmosis

Ring-enhancing lesions seen in the brain parenchyma on contrast-enhanced CT scan of the head, with clinical response to sulphadoxine and pyrimethamine (anti-*Toxoplasma* therapy).

Wherever there was no microbiological or histopathological confirmation of the final diagnosis, the patients were included only if they had typical clinical features of the particular disease, other pathogens had been ruled out and the patients responded to appropriate antimicrobial therapy for the particular disease state.

Analysis

The frequency of occurrence of the defined diseases in the 3 groups, with their specific clinical and laboratory characteristics, were noted. The absolute lymphocyte count (ALC) inferred from the percentages of the total and differential white blood cell counts was correlated with the AIDS-defining illnesses [as per the Centers for Disease Control (CDC) expanded surveillance case definition 1993].

Following a retrospective case series analysis done in September 1996 of 35 HIV-infected patients with prolonged fever, the prevalence of TB among them was found to be 42%. We therefore calculated that a sample size of 94 adult patients with prolonged fever would be needed to obtain a definitive diagnosis in at least 50% of them. Summary statistics and tests of significance (Chi-square test for categorical variables and Student *t* test for continuous variables) were calculated using the software package SPSS version 9 on an IBM-compatible PC.

RESULTS

The 100 HIV-infected patients with prolonged fever seen during this 20-month period had a mean age of 35 years (range: 20–60 years) and a male predominance (88%). None were parenteral drug users and the vast majority were deemed to have acquired the infection through heterosexual contact.

Overall, 25 patients had prolonged fever alone (group 1), 54 had prolonged fever with respiratory symptoms (group 2), and 21 had prolonged fever with neurological symptoms (group 3). The baseline clinical and laboratory characteristics of the patients within each of the three groups (Table I) were similar, except that oral candidiasis was less frequently seen in patients belonging to group 3. None of the patients received ART nor did they receive primary prophylaxis against *M. tuberculosis, P. carinii, C. neoformans* or *T. gondii.*

Table II shows that TB was the commonest cause for prolonged fever (69%) in each of the 3 groups. The diagnosis of TB was confirmed by the presence (in sputum) of AFB in 8 patients, and histopathological evidence of granulomas or AFB (bone marrow, lymph node FNA or liver biopsy) in 47 patients. In 14 patients the diagnosis was made on clinical grounds as defined in the methodology. Cultures were subsequently positive for *M. tuberculosis* in specimens of the bone marrow and sputum of 12 patients. Disseminated TB was the most common form of tuberculosis occurring in 43 patients and presented commonly as fever alone or fever with cough. The other important clinical findings noted in these patients were weight loss in 32, hepatomegaly in 19, and splenomegaly and lymphadenopathy in 11 each. The abnormal investigations characteristic of disseminated TB were anaemia (haemoglobin <8 g/dl) in 21, lymphopenia (<1000/cmm) in 30 patients and a raised alkaline phosphatase level (>125 U/L) in 26.

Seven patients were diagnosed to have PCP, of whom 1 belonged to group 1 and 6 to group 2. Six had a chest X-ray

TABLE I. Clinical and laboratory profile of the 100 HIV-infected patients with prolonged fever

Clinical and laboratory parameter	Group 1 (*n*=25)	Group 2 (*n*=54)	Group 3 (*n*=21)
Weight loss (reported significant)	18 (72)	44 (81)	16 (76)
Lymph node enlargement	16 (64)	30 (56)	6 (28)
Palpable hepatomegaly	15 (60)	16 (30)	5 (24)
Oral candidiasis	10 (40)	22 (41)	5 (24)
Palpable splenomegaly	5 (20)	7 (13)	1 (4.8)
Anaemia (haemoglobin <8 g/dl)	9 (36)	21 (39)	6 (28)
Leucopenia (WBC <4000/cmm)	6 (24)	9 (17)	3 (14)
Absolute lymphocyte count			
<1000/cmm	2 (48)	31 (57)	8 (38)
>1000/cmm	10 (40)	22 (41)	11 (52)
Alkaline phosphatase (>125 U/L)	15 60)	23 (43)	7 (33)
Lactate dehydrogenase (>400 U/L)	2 (8)	11 (21)	3 (14)

* Done in 94 patients   Values in parentheses are percentages

TABLE II. Aetiology of prolonged fever in 100 HIV-infected patients with no prior antiretroviral therapy or primary prophylaxis

Aetiology	Group 1 (*n*=25)	Group 2 (*n*=54)	Group 3 (*n*=21)	Total (*n*=100)
Tuberculosis				
Disseminated	15	21	7	43
Pulmonary	2	13	1	16
Extrapulmonary	5	4	1	10*
Pneumocystis carinii pneumonia	1	6	0	7
Cryptococcosis	0	3	7	10†
Toxoplasmosis	0	0	1	1
Liver abscess	1	1	0	2
Community-acquired pneumonia	0	2	0	2
Disseminated histoplasmosis	0	1	0	1
Miscellaneous	1	1	2	4‡
No aetiology	0	2	2	4§

* Eight patients with lymphadenitis; one each with meningitis and peritonitis
† Seven patients with meningitis and three with disseminated disease
‡ One patient each with malaria, bacterial meningitis, sinusitis and spontaneous bacterial peritonitis
§ Fever disappeared in two patients, and two were discharged against medical advice

showing an interstitial pneumonia pattern and they responded to therapy. The diagnosis in the seventh patient with subsegmental infiltrates on chest X-ray who did not respond to therapy was confirmed on a postmortem lung biopsy. Arterial blood gas analysis showed hypoxaemia in 6 patients. The DFA test was negative for *P. carinii* antigen in the induced sputum smears of all patients. PCP was not seen among the patients in group 3.

Among those diagnosed to have crytococcosis (in groups 2 and 3), culture was positive for *Cryptococcus* spp. in all the 10 patients (CSF 9, sputum 2 and blood 1). There were 3 patients with disseminated cryptococcosis and, in 2 of these, the organism was isolated from more than one site (sputum and CSF), and in the other, from blood alone (the CSF was sterile).

Other less common OI included cerebral toxoplasmosis in 1 patient (group 3) who improved on therapy, and disseminated histoplasmosis in another (group 2) who succumbed during the hospital stay. Of the 2 patients diagnosed to have community-acquired pneumonia, *Streptococcus pneumoniae* was isolated from the sputum of 1 and in the other no pathogen could be detected either in the sputum or on blood culture. However, both responded to parenterally administered penicillin G. The 2 patients with liver abscess improved with metronidazole suggesting

a possible aetiological role for either *Entamoeba histolytica* or anaerobic organisms.

ALC values <1000/cmm predicted AIDS accurately in 45 patients and could not do so in 36 others and thus had a low sensitivity of 55%, but a positive predictive value of 85% in diagnosing AIDS (Table III). A higher occurrence of tuberculosis was noted if the ALC was <1000/cmm.

In 62 of our cases, we required invasive tests such as FNA of the lymph node (28 patients), biopsies of the bone marrow and liver (13), lumbar puncture (12), abdominal paracentesis (2) and arterial blood gas estimation (7) to establish a definitive diagnosis. The lymph node FNA showed granulomas with AFB in 4 patients, granulomas without AFB in 3 and AFB without granulomas in 21 patients. In the bone marrow trephine core biopsy, granulomas were seen in 8 patients, and granulomas with AFB in 2. Liver biopsy (done in 3 patients) revealed histoplasmosis in 1 and TB in another. The procedure did not provide a definitive diagnosis in 1 patient.

Non-invasive tests such as ultrasound of the abdomen (21), chest X-ray (13) and CT scan of the head (1) were done in the remaining patients. In some instances an ultrasound helped us to localize the abdominal lymph nodes for the FNA procedure. The findings seen on ultrasound of the abdomen were lymphadenopathy alone (7 patients), lymphadenopathy with hepatosplenomegaly (6), lymphadenopathy with hypoechoic areas in the liver and spleen (4), hepatosplenomegaly (4), and liver abscesses and loculated ascites (2 each). The diagnostic yields of ultrasound of the abdomen, lymph node FNA cytology/biopsy and bone marrow trephine biopsy were 85%, 75.6% and 41.6%, respectively.

DISCUSSION

This is a large case series documenting the clinical features and aetiology of prolonged fever occurring among HIV-infected individuals in India. Infections were the commonest and TB was the most important aetiological factor in our study. Disseminated, extra-pulmonary and pulmonary forms of TB occurred in 69% of the patients who had fever as the primary manifestation, and this seems to be consistent with the clinical profile described in other series reported from India.[9,10] This finding is not surprising as TB is still the commonest infection that causes prolonged fever even among the non-HIV infected population in India.[11,12]

The other major opportunistic fungi causing prolonged fever were *P. carinii, Cryptococcus* spp. and *Histoplasma capsulatum.* Induced sputum was negative for *P. carinii* by DFA in all our patients diagnosed to have PCP, which is similar to the reported experience from other centres in India.[13] DFA for *P. carinii* antigen has been reported to have a sensitivity of 85% in other studies perhaps due to a better test performance or sputum induction.[14,15] An elevated level of serum LDH (>400 U/L) was seen in 4 patients, a non-specific finding in keeping with earlier observations.[16] In the absence of a definite pathogen, bacterial pneumonias may have been a possibility in these patients but cultures were negative for easily cultivable pathogens, and 6 of 7 patients

responded to anti-PCP (co-trimoxazole) therapy. One patient died despite therapy. However, the diagnosis in this patient was confirmed by a postmortem lung biopsy.

Cryptococcosis was seen in 10% of our patients; this finding was similar to that of other studies from India which have reported a prevalence ranging from 1% to 7% among HIV-infected individuals.[9,10] Among those with cryptococcal meningitis, an India ink preparation and detection of antigen in the CSF provided a definitive diagnosis in 9 out of 10 patients. Only 1 patient with a negative smear and antigen was subsequently proven to have cryptococcosis on CSF fungal culture. One patient had disseminated histoplasmosis, the other important fungal infection seen in HIV-infected patients.

We did not detect disseminated *M. avium intracellulare* (MAI) or cytomegalovirus (CMV) infections among our patients. It has been postulated that prior infection with *M. tuberculosis* probably confers protection against other atypical mycobacterial species.[17] It is also possible that most of the HIV-infected population in developing countries do not survive until the stage of severe immunodeficiency (CD4 cell counts <50/cmm), when the chance of developing MAI or CMV infection is high.

ALC values <1000/cmm had a good positive predictive value (85%) for the diagnosis of AIDS in our study, similar to the reported experience from another centre in India.[13]

Ultrasound of the abdomen, lymph node FNA cytology/biopsy and bone marrow trephine biopsy studies were the most useful among the investigative procedures in our study, providing high diagnostic yields, especially when clinical diagnostic clues were lacking. Liver biopsy yielded the diagnosis when it was not obtainable after these tests. These four tests with histopathological examination led to a precise diagnosis sooner than would otherwise have been possible, if mycobacterial or fungal culture reports were awaited.[19,20] Our results confirm that lymph node FNA cytology/biopsy should be the invasive procedure of choice when clinically marked peripheral lymphadenopathy is present. Subsequently, an ultrasound of the abdomen or chest X-ray would help to locate the enlarged lymph nodes in these areas for an FNA cytology/biopsy. If the yield from these three procedures is negative, other invasive procedures such as bone marrow trephine biopsy or needle biopsy of the liver would be required to confirm the cause of the fever. Therefore, based on our results, we have proposed a modified version of the JHU algorithms for evaluation of adult, antiretroviral-naïve, HIV-infected Indian patients with prolonged fever (Figs 1, 2 and 3). As TB was the most important cause, the modified algorithms have been focused to detect TB, as well as the other important pathogens seen in our study.

Limitations of the study

This study has its limitations in that it was a hospital-based cohort, which included a convenient, non-consecutive, non-probability sample, and therefore it may not be possible to generalize the findings to patients with protracted fever seen in smaller community hospitals. We suggest simple algorithms for the management of patients with prolonged fever. However, we recognize that the algorithms for the evaluation of patients with respiratory and neurological symptoms may not be data driven as we had insufficient numbers. These may be useful approaches in resource-limited clinical settings, recognizing that the lack of improvement or a negative evaluation may require referral to a higher centre.

Even as antiretrovirals become more affordable and their use—along with primary and secondary prophylaxis for various OI—becomes widespread, prolonged fever will continue to be an

TABLE III. Absolute lymphocyte counts and diagnosis of AIDS in 94 HIV-infected patients with prolonged fever

Absolute lymphocyte count	AIDS* (*n*=81)	No AIDS (*n*=13)
<1000/cmm	45	6
>1000/cmm	36	7

*AIDS as defined by the Centers for Disease Control expanded surveillance case definition
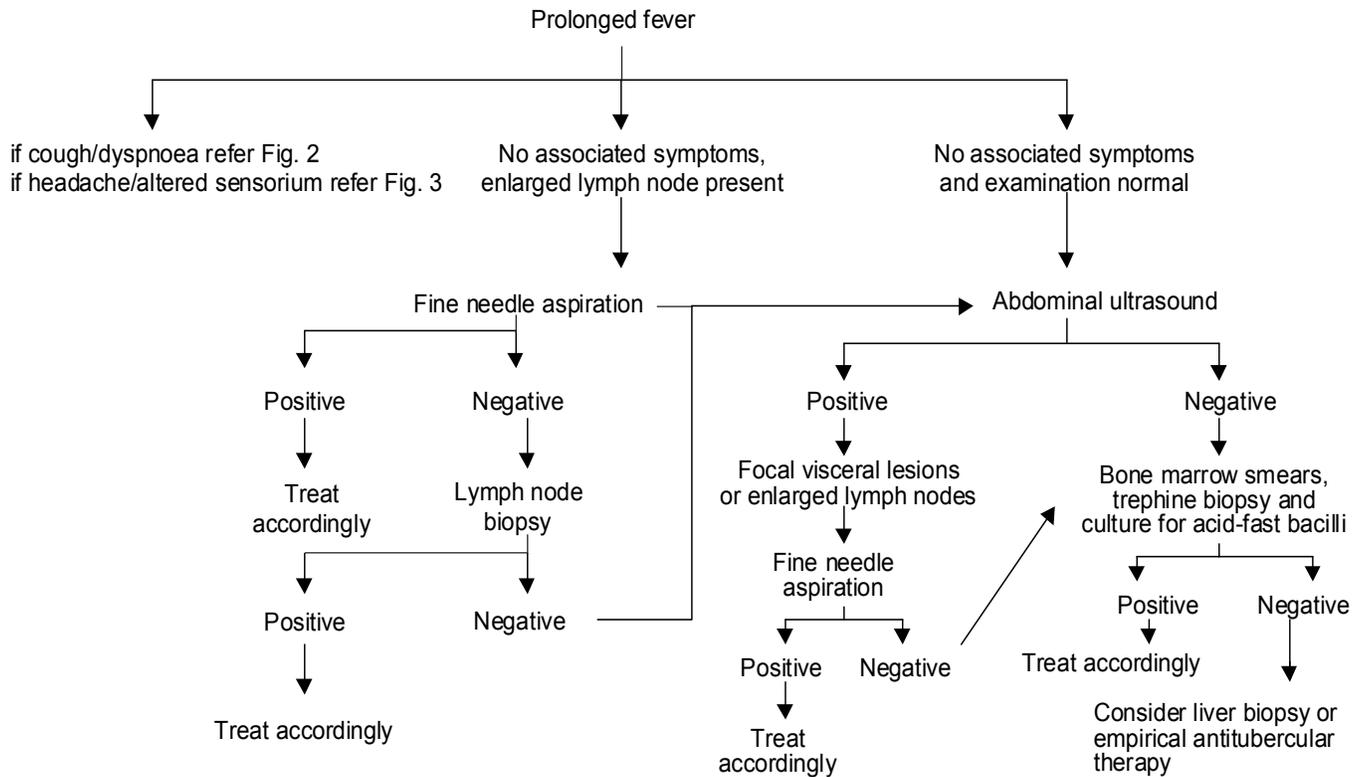
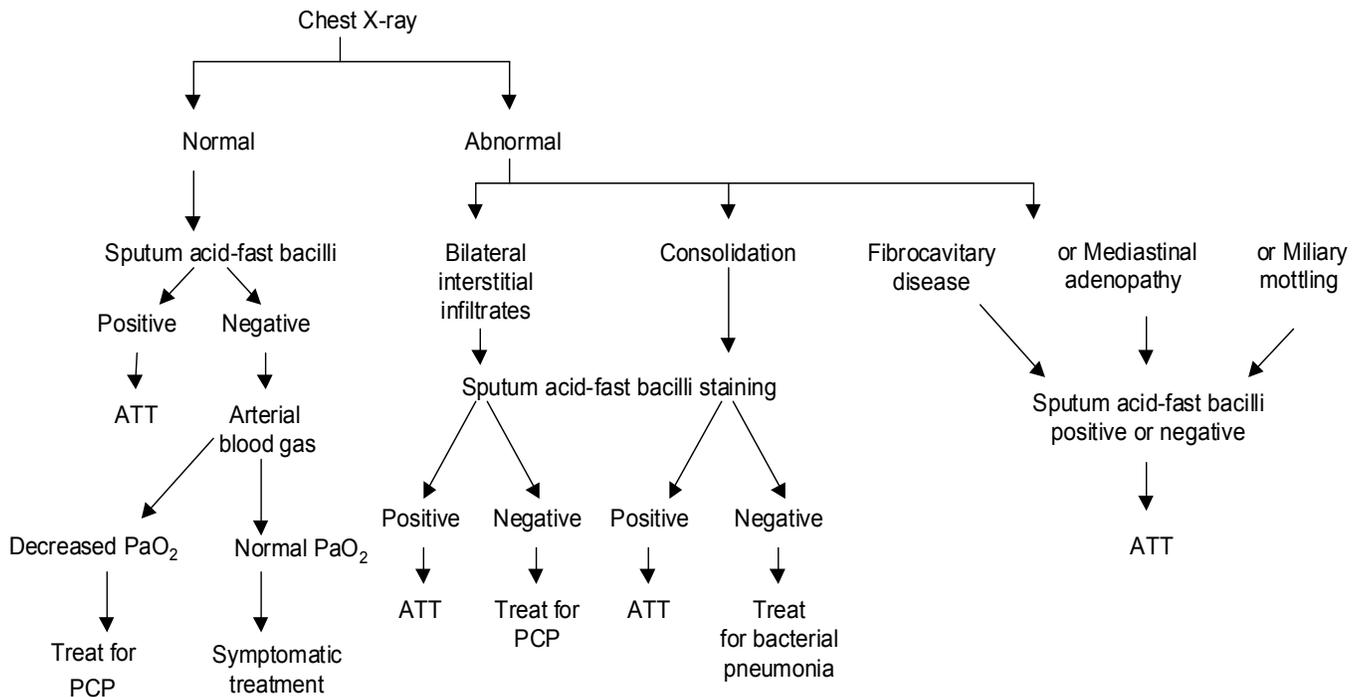FIG 1. Management algorithm for HIV-infected patients with prolonged fever

FIG 2. Management algorithm for HIV-infected patients with prolonged fever and pulmonary symptoms. PaO$_2$ partial pressure of oxygen (mmHg)   PCP *Pneumocystis carinii* pneumonia   ATT antitubercular therapy
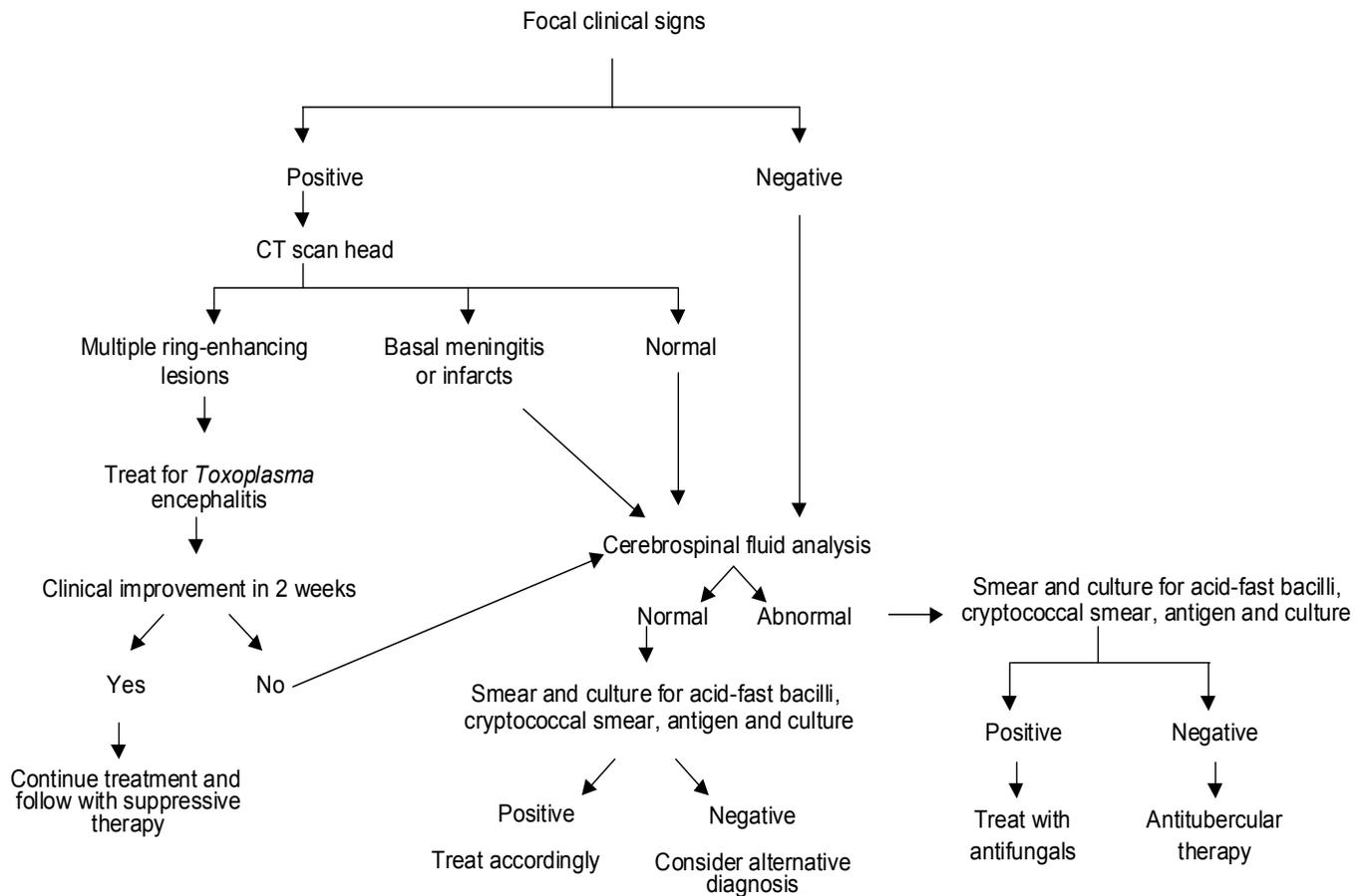
FIG 3. Management algorithm for HIV-infected patients with prolonged fever and neurological symptoms   CT computed tomography

important presenting symptom. We will need an additional series to see how these, and the use of rapid diagnostic tests such as polymerase chain reaction, especially for TB, will impact the clinical spectrum.

In conclusion, among HIV-infected patients with prolonged fever, infection is the cause in the vast majority; with over two-thirds being due to TB. If non-invasive tests are unrewarding, an algorithm that judiciously utilizes invasive tests such as lymph node FNA cytology/biopsy and needle biopsies of the bone marrow and liver will be appropriate. However, among patients with only prolonged fever and no specific clinical finding, if the initial non-invasive tests are non-contributory and further invasive tests are not feasible, a therapeutic trial of ATT is justified before referral to a centre with facilities for further evaluation.[21]

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Human Immunodeficiency Virus (HIV). Molecular Biologist Greg Towers on how HIV is transmitted, the possibilities of an HIV vaccine, and how it helps understand our immune system better. faq | November 29, 2016. HIV-1(M) has evolved to transmit very effectively between people as a sexually transmitted disease and we don't understand why this virus can transmit so effectively, whereas the other viruses do not. It suggests that it is very difficult for a virus to adapt to human-to-human transmission, even when it comes from a very closely related species, such as chimps. This helps explain why new viruses infecting many humans are rare. Causes of HIV. HIV entry into T Cell (Wikipedia.org). These guidelines provide guidance on the diagnosis of human immunodeficiency virus (HIV) infection, the use of antiretroviral (ARV) drugs for treating and preventing HIV infection and the care of people living with HIV. They are structured along the continuum of HIV testing, prevention, treatment and care. This edition updates the 2013 consolidated guidelines on the use of antiretroviral drugs following an extensive review of evidence and consultations in mid-2015, shared at the end of 2015, and now published in full in 2016. It is being published in a changing global context for HIV and for h Quantitative Human Immunodeficiency Virus (HIV)-1 Antibodies Correlate With Plasma HIV-1 RNA and Cell-associated DNA Levels in Children on Antiretroviral Therapy. This study measured serial plasma human immunodeficiency virus (HIV)-1-specific antibody (Ab) levels in children who initiated antiretroviral therapy (ART) prior to 2 years of age, and evaluated their... Hiv-associated Lipodystrophy Syndrome. Defective metabolism leading to fat maldistribution in patients infected with HIV. The etiology appears to be multifactorial and probably involves some combination of infection-induced alterations in metabolism, direct effects of antiretroviral therapy, and patient-related factors. Antiretroviral Therapy, Highly Active.