# Is it HIV?

## A handbook for health care providers

ashm
Australasian Society for HIV Medicine

TREATASIA

Edited by: Arun Menon
Adeeba Kamarulzaman

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# Preface

It is with a great sense of appreciation that the Australasian Society for HIV Medicine (ASHM) and TREAT Asia jointly bring you this publication. It is the result of considerable dedicated work and perseverance.

ASHM produced a similar publication *Could It Be HIV?* in Australia in 1993. That served as a durable text for clinicians in making a differential diagnosis of HIV, often in the context of opportunistic infection. The publication was distributed as a monograph by the Medical Journal of Australia, and reprinted in 1994. In 2002 ASHM changed to a new format when it published *HIV, Viral Hepatitis and STI: A guide for primary care*, which serves as a basic text for our clinical education program.

Then, ASHM ran its first regional Short Course in HIV Medicine in Sydney in 2002. The need for a more regionally-focused clinical text was identified, and initial discussions to achieve this goal began with TREAT Asia at the ASHM Conference in Cairns in 2003.

The resultant publication is a true partnership, and could not have come about without the contributions of the many supporters of ASHM's educational mission and members of the TREAT Asia network.

We are confident that this book will assist in the education of health care providers in HIV medicine in the Asian and Pacific regions, and act as a useful reference for those already working in the field. We also hope it will serve as a catalyst for future joint initiatives aimed at supporting health care providers and assisting them to deliver optimal care to their patients living with HIV.

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# 1 Introduction

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**The objective of this handbook is to enhance awareness and familiarise health care providers with different clinical presentations of human immunodeficiency virus (HIV)-related disease so that they can recognise the possibility of HIV infection and recommend testing where appropriate.**

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimates, about 4.9 million people were living with HIV in Asia in 2007 including 440 000 people who newly acquired the infection in the past year. In the Pacific region, an estimated 75 000 people are living with the virus with 14 000 having acquired the infection in 2007. In this region, Papua New Guinea (PNG) has the largest burden of disease having over 70% of the total number of people living with HIV in the Pacific.[1]

A large proportion of individuals with HIV infection are not aware of their HIV status and present to the health care system at an advanced stage of the disease, when treatment response is less favourable.[2,3] Late presentation may partly be due to low levels of awareness of the personal risk of HIV infection or concern about discrimination and stigmatisation, both of which can deter people from undergoing testing. On the other hand, there could also be lost opportunities for early diagnosis of HIV infection when patients present to health care providers due to lack of provider experience with common clinical scenarios in people with HIV infection at different stages of their disease.

Early detection of HIV infection is important for many reasons. Counselling and interventions can be implemented to prevent subsequent transmission of HIV to others.

Risk reduction measures that can be reinforced include consistent use of condoms, avoidance of needle sharing and use of antiretroviral drugs to prevent mother-to-child transmission. A patient presenting with early stage HIV infection can be closely monitored so that combination antiretroviral therapy (cART) can be started at the appropriate time to prevent disease progression.

Knowledge about the prevailing epidemiology of HIV infection in each locality would be helpful to enhance the awareness of health care workers. In Asia, the epidemic was initially recognised through sporadic cases involving sexual contact with foreigners or use of contaminated blood products. By 1988, a rapid surge in HIV infection was noted among injecting drug users and later female commercial sex workers in a number of Asian countries. Currently, the prevalence rates of HIV infection among these two groups in many Asian countries have reached more than 10% and, in some cities, the rates are higher than 60%.[1] HIV has thus become established within Asia and continues to spread throughout the region.

The HIV epidemic in the Asian and Pacific regions reflects the broad diversity in ethnicity, cultural expectations, religious practices and socio-economic profile, as well as levels of health care infrastructure. With heterosexual transmission being the predominant mode of infection, there is a greater proportion of women among those with the infection than in Western countries and many countries are seeing increasing numbers of children born with HIV. As a result of infection among clients of female commercial sex workers and their regular partners, HIV infection has also spread beyond the traditionally recognised risk groups to the general population.

In the past few years, the regions have also witnessed a surge in the numbers of HIV infections among men who have sex with men.[4] As an illustration, the United Nations General Assembly Special Session (UNGASS) country progress report by Thailand showed that the majority of new HIV infections in Thailand occurred among spouses of individuals with HIV as well as men who have sex with men.[5]

The majority of notifications for HIV in the Pacific are from PNG where the main mode of HIV transmission appears to be heterosexual intercourse, with high rates of unsafe anal and vaginal sex with multiple partners, and the frequent failure to use condoms.[1]

It is important to recognise that the majority of people with HIV remain asymptomatic during a long incubation period which averages up to 10 years. Health care workers should include questions about possible HIV risk behaviours in the routine clinical assessment of their patients. This assessment should involve obtaining a history of: sexually transmissible infections, unprotected sexual contact with a partner of the same or opposite gender with unknown HIV status, or re-use of drug injecting equipment. The risk is higher with multiple or casual partners. For those with a regular partner, obtaining information about the behaviour of their partner may also be relevant.

Once HIV risk has been identified, the patient should be encouraged to undergo HIV testing with adequate counselling and support. It should be emphasised that HIV risk assessment should be undertaken in a sensitive and non-judgmental manner, so that patients are encouraged to openly discuss their concerns with their health care providers. In addition, sensitive information is confidential and the HIV risk behaviour or infection status should not result in any discriminatory treatment to the patient.

Primary HIV infection may present with the clinical picture of a febrile illness approximately 2–4 weeks after exposure. The symptoms may include skin rash, myalgia, fatigue, sore throat, diarrhoea, lymphadenopathy, hepatosplenomegaly and, rarely, neurological symptoms. While this seroconversion illness may occur in up to 70–80% of individuals, it is often not viewed as serious or related to HIV infection, due in part to its self-limited course.

Primary HIV infection seldom results in presentation to health care settings. Patients with any combination of the above symptoms should be asked about a history of recent unprotected sexual activity or injecting drug use. It is crucial to try and identify patients with acute HIV infection, as they have very high HIV viral loads and are extremely infectious. Management may include general supportive measures for physical, psychological and social issues. The role of antiretroviral therapy in acute HIV infection remains controversial.

When the immune system becomes progressively damaged by HIV, reflected by a steady decline of the CD4 lymphocyte count to 200 – 350 cells/μL, the patient may develop symptoms that are commonly associated with HIV disease. These include persistent fever, night sweats, significant weight loss, oral thrush, herpes zoster and chronic diarrhoea. Thrombocytopenia and lymphopenia may be present on blood testing. When these are present in combination without any other underlying cause, the possibility of HIV infection should be considered and HIV testing recommended. Another clinical scenario when HIV infection should be suspected is when a person presents with an infection commonly seen in that setting, but the clinical course is exceptionally severe or resistant to standard therapies. In recent years, it has also been recognised that HIV infection can predispose to renal and cardiovascular disease as well as malignancies at CD4 lymphocyte counts over 200 cells/μL. HIV can also affect the nervous system directly causing cognitive impairment.

With further decline of the CD4 lymphocyte count to below 200 cells/μL, the patient will become prone to a number of opportunistic infections which rarely occur in individuals with intact immune function. It is important to recognise that the pattern of opportunistic infections in Asia is frequently different from that seen in Western countries, with a predominance of tuberculosis followed by *Pneumocystis jirovecii* pneumonia. Cryptococcal meningitis is the most common opportunistic infection affecting the nervous system. Specific to part of the region is disseminated disease caused by *Penicillium marneffei*, a fungus endemic in Thailand and part of southern China.[6] On the other hand, it is possible that some opportunistic diseases are under-diagnosed due to inadequate access to diagnostic testing.

It should be noted that any organ system can become involved in opportunistic infections and the clinical presentation of acquired immunodeficiency syndrome (AIDS) is therefore highly variable. Health care providers in various clinical specialties may have patients with HIV infection in their practices and should be aware of the possible clinical presentation.

With the move to early HIV diagnosis and the instigation of antiretroviral treatment programs in the Asia and Pacific regions, there are a number of other issues that are beyond the scope of this handbook that need to be addressed. Doctors and nurses will require appropriate training to be able to manage treatment side effects and to support drug adherence.

Access to timely CD4 lymphocyte count and viral load testing is crucial to monitor the response to cART and detect treatment failure at an early stage. The greatest challenge lies in reaching patients living in remote rural areas, as clinical expertise tends to be concentrated in big cities. Collaboration with non-government organisations and patient empowerment programs is a key element to ensure the successful initiation of antiretroviral treatment.


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# References


1. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). 2007 AIDS epidemic update. Geneva: UNAIDS, December 2007.

2. World Health Organization (WHO). Progress report April 2007: Toward universal access: scaling up priority HIV/AIDS interventions in the health sector.

   Available at:
   http://searo.who.int/en/Section10/Section18/Section2008_13202.htm (Last accessed 20 September 2009).

3. Zhou J, Kumarasamy N, Ditangco R, Kamarulzaman A, Lee CK, Li PC, et al. TREAT Asia HIV Observational Database. The TREAT Asia HIV Observational Database: baseline and retrospective data. J Acquir Immune Defic Syndr 2005;38:174-9.

4. Van Griensven F, de Lind van Wijngaarden JW, Baral S, Grulich A. The global epidemic of HIV infection among men who have sex with men. Curr Opin HIV AIDS 2009;4(4):300-7.

5. UNGASS Country Progress Report, Thailand. Reporting period: January 2006-December 2007.

   Available at:
   http://data.unaids.org/pub/Report/2008/thailand_2008_country_progress_report_en.pdf (Last accessed 20 September 2009).

6. Ustianowski AP, Sieu TP, Day JN. *Penicillium marneffei* infection in HIV. Curr Opin Infect Dis 2008;21:31-6.

# 2 HIV seroconversion illness

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## Introduction

Diagnosis of human immunodeficiency virus (HIV) infection especially in its early stage, i.e. primary HIV infection, remains a challenging task for health care providers. Although primary HIV infection (also called HIV seroconversion illness or acute retroviral syndrome) has been described since 1985,[1] the condition, which encompasses all acute and recent HIV infection (within 6-12 months), frequently remains misdiagnosed or underdiagnosed.[2-4] This misdiagnosis is primarily due to the non-specific features of the illness, inadequate history taking and a low index of suspicion by clinicians and inadequate interpretation of serology testing results.[5,6]

Diagnosing primary HIV infection is important for several reasons. Firstly, it is well recognised that a person with primary HIV infection is highly infectious because primary HIV infection represents a period of extremely high levels of viraemia and genital shedding of the virus.[7-11] It has been shown that an HIV diagnosis can result in subsequent risk reduction in individuals with HIV infection.[12] Thus, early identification of primary HIV infection may result in behavioural changes in these individuals with HIV thereby minimising further transmission of the infection. From the perspective of a person with the infection, evidence suggests that the magnitude of the viral load set point during primary HIV infection and more severe acute HIV illness has been shown to be predictive of faster disease progression.[13,14] Early recognition of primary HIV infection provides a window of opportunity to change the course of the disease for the individual. Although systematic initiation of antiretroviral therapy during primary HIV infection remains controversial, emerging evidence supports its potential virological, immunological and clinical benefits, apart from the important public health consideration associated with risk reduction in HIV transmission.[15-19]

The potential advantages of early intervention and treatment include reduced risk of viral transmission, decreased severity of the symptoms of the acute infection, limitation of viral mutation, earlier decay of cellular reservoirs and prolongation of the total time patients can remain off chronic therapy.[15-19] These theoretic benefits of early treatment must be weighed against the possible risks, including higher risk of long-term antiretroviral drug toxicities due to a considerable increase in the duration of antiretroviral exposure and evolution of drug resistance if therapy fails to completely suppress viral replication. In the absence of a clear consensus on treatment for the acutely infected, the decision to initiate or defer treatment must be individualized and the pros and cons of treatment discussed with the patient.

## Clinical features

The clinical features of acute retroviral syndrome are non-specific. An acute infectious mononucleosis-like illness occurs in up to 93% of patients but many organ systems can be affected, causing a wide array of symptoms and signs mimicking other clinical entities (Table 2.1).[20]

**Table 2.1: Differential diagnoses associated with primary HIV-1 infection**

| Infectious | |
|---|---|
| *Viral* | *Bacterial* |
| Epstein Barr virus<br>Cytomegalovirus<br>Primary herpes simplex infection<br>Influenza | Streptococcal disease<br>Secondary syphilis<br>Typhoid<br>Leptospirosis |

Continued over page

| Table 2.1: Differential diagnoses associated with primary HIV-1 infection (Continued) | |
|---|---|
| Dengue<br>Chikungunya<br>Early stage viral hepatitis | Lyme disease<br>Rickettsial diseases<br>Disseminated gonococcal infection |
| Parvovirus B19 | *Parasitic* |
| Rubella | Acute toxoplasmosis<br>Malaria |
| Non-infectious | |
| Systemic lupus erythematosus<br>Adult Still's disease<br>Systemic vasculitides<br>Drug reaction | |

Constitutional symptoms of fever, malaise or fatigue, anorexia, weight loss, maculopapular skin rash, mucosal membrane ulcerations, pharyngitis and diffuse lymphadenopathy are common infectious mononucleosis-like manifestations. Gastrointestinal symptoms such as nausea, vomiting and diarrhoea, pulmonary symptoms such as productive cough (which occasionally can be due to pneumocystis pneumonia); neurological and psychiatric symptoms such as headache, meningitis, encephalitic or meningoencephalitic presentations; haematological abnormalities such as leucopenia, lymphopenia and thrombocytopenia; and liver involvement with raised transaminases have all been described.[3,13,20,21-23] Occasionally, renal involvement with lupus-like glomerulonephritis and rarely, rhabdomyolysis and cold agglutination haemolysis can occur.[20] A case of multiple organ failure during primary HIV infection has been recently reported.[24]

It is estimated that 40-90% of patients with primary HIV infection experience acute retroviral syndrome.[13, 21-23] The development of acute retroviral syndrome typically coincides with high levels of viraemia and the host's initial immunological response. Symptoms typically occur 2–6 weeks after exposure and last for 14 days but may persist for as long as 10 weeks.[13, 21-23] The formation of HIV-1–specific antibodies marks the completion of seroconversion; antibodies are generally detectable by weeks 3–12 of infection but may take up to 6–12 months to form.[25]

## Where does the patient present?

Primary care facilities, emergency department, walk in clinics and dermatology clinics are among the most frequently attended facilities by people with acute retroviral syndrome.[2,4,22] However, because of its non-specific and protean manifestations, patients may also present to other units such as neurology, gastroenterology, psychiatry, respiratory and genitourinary, depending on the individual presentation.

## When does the patient present?

Febrile illness is the most common problem that leads to seeking medical attention. Patients may also seek medical care if they develop organ-related complications or impairment. HIV infection should always be considered in a person with a history of exposure to another person with known or possible HIV infection, and in a person with any of the following diagnostic flags (Table 2.2).[13]

| Table 2.2: Diagnostic flags for HIV infection |
|---|
| Febrile illness with mucocutaneous rash |
| Acute meningoencephalitis syndrome or aseptic meningitis |
| Mucocutaneous ulcerations involving buccal mucosa, gingival, palate, oesophagus, anus or penis |
| Any unexplained severe febrile illness |
| Febrile illness with leucopenia, lymphopenia, thrombocytopenia with or without raised transaminases |
| A person presenting with sexually transmitted infections |

# Difficulties in making the diagnosis

## Inadequate risk assessment

In a cohort of 46 patients with primary HIV infection, more than 85% sought medical attention but only 25% received the correct diagnosis.[22] In a recent study, diagnosis of primary HIV infection was not made in 48% of patients at first presentation.[4] Acute retroviral syndrome has been reported to be confused with a variety of other illnesses, including infectious mononucleosis, secondary syphilis and other common and important tropical and subtropical infections such as typhus, dengue and leptospirosis.[26-28] This confusion is of particular concern because the disease burden of dengue, typhus and leptospirosis is high in the Asian and Pacific regions and many patients are treated presumptively for those conditions on clinical grounds.

Adding to the problem is the lack of laboratory facilities to make the laboratory confirmation of these various infectious diseases. Thus, the opportunity of making a diagnosis of primary HIV infection may easily be missed if the index of suspicion is low and if history taking is lacking, especially for sexual and drug use history.

## Inadequate interpretation of laboratory test results

See laboratory diagnosis of HIV infection chapter for rapid testing.

**Case study 2.1 Dengue infection or acute HIV seroconversion illness**

A 31-year-old single man was admitted with a 10-day history of fever associated with myalgia, headache, nausea, vomiting, anorexia, malaise and skin rash. Physical examination revealed generalised maculopapular rash and a few petechiae. His full blood count showed Hb: 15.6 g/dL, Hct: 44%, WBC: 3.1x $10^9$/L (63% PMN, 30% LYMP, 5% M); platelet count: 85 x $10^9$/L.

His liver function tests showed: AST: 103 IU/L, ALT: 85 IU/L. A clinical diagnosis of dengue fever was made. He was given fluid support and discharged home a day later, as he was thought to have recovered from dengue infection when his fever subsided.

Four days later, he returned with persistent fever, vomiting, and oral ulcers. Physical examination revealed generalised maculopapular rash, oral ulcerations with gum bleeding and cervical lymphadenopathy. There were no other remarkable findings. He did not have a recent history of travelling or jungle trekking.

With further enquiry, he admitted to having had unprotected sexual contact with a male partner about four weeks before the onset of his symptoms. At this time, his full blood count revealed Hb: 16 g/dL, Hct: 46%, WBC: 4.0 x $10^9$/L (62% PMN, 25% LYMP, 10% M, 3% AL); platelet count: 132 x $10^9$/L. His liver function tests showed: AST: 480 IU/L, ALT: 393 IU/L. Blood culture, monospot test, screening tests for dengue, leptospirosis, typhus, typhoid and malaria were all negative.

He was counselled for HIV testing. An HIV Combo ELISA test (p24 antigen + HIV antibody) was done and reported to be reactive. HIV ELISA, particle agglutination tests were carried out and were not reactive.

In view of his recent unprotected sexual exposure and his laboratory results, a diagnosis of acute HIV seroconversion illness was made. A repeat HIV antibody test was performed about 7 days later and showed a positive reaction, indicating acute seroconversion. His CD4 cell count (and percentage) was reported to be 231 (11%) cells/μL and his HIV-1 viral load was greater than 100 000 copies/mL.

**Case discussion**

This case illustrates clearly that acute retroviral syndrome can be easily misdiagnosed as dengue illness due to overlapping clinical and laboratory features. The infectious mononucleosis-like illness as the presenting feature is indistinguishable between these two entities, as is the skin rash. This case resulted in further confusion with the presence of leucopenia, thrombocytopenia, and raised transaminases, which are also common findings in dengue. [29]

All these features underscore the importance of obtaining an adequate history, including a sexual history, in dealing with acute onset febrile illness in countries with tropical and subtropical settings. Table 2.3 provides some clues that may be helpful in differentiating dengue from acute retroviral syndrome.

**Table 2.3: Summary of differentiating features of dengue and acute HIV seroconversion illness**

| Features | Dengue | Acute retroviral syndrome |
|---|---|---|
| Fever<br>Average duration of fever<br>Range | Yes<br>Less than 7 days<br>2-10 days | Yes<br>Usually less than 14 days<br>Several days to more than 10 weeks |
| Skin rash | Yes | Yes |
| Plasma leakage/shock | Hallmarks of DHF/DSS * | Absent |
| Bleeding manifestations | Yes, typical feature of DHF/DSS * | Not a typical feature |
| Leukopenia | Transient and brief | May be prolonged |
| Thrombocytopenia | Transient and brief | May be prolonged |
| Raised transaminases | Transient and brief | May be prolonged |
| Recent exposure to HIV-1 (such as but not limited to unprotected sex) | Not relevant | Crucial history |

* DHF Dengue haemorrhagic fever
* DSS Dengue shock syndrome

# References


1 Cooper DA, Gold J, Maclean P, Donovan B, Finlayson R, Barnes TG, et al. Acute AIDS retrovirus infection. Definition of a clinical illness associated with seroconversion. Lancet 1985;1;537-40.

2. Weintrob AC, Giner J, Menezes P, Patrick E, Benjamin DK Jr, Lennox J, etal. Infrequent diagnosis of primary human immunodeficiency virus infection:missed opportunities in acute care setting. Arch Intern Med 2003;163:2097-100.

3. Zetola NM, Pilcher CD. Diagnosis and management of acute HIV infection. Infect Dis Clin North Am 2007; 21:19-48.

4. Sudarshi D, Pao D, Murphy G, Parry J, Dean G, Fisher M. Missed opportunities for diagnosing primary HIV infection. Sex Transm Infect 2008;84(1):14-6.

5. Flanigan T, Tashima KT. Diagnosis of acute HIV infection:it's time to get moving! Ann Intern Med 2001; 134 (1):75-7.

6. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med 1996;125:257–64 (erratum: Ann Intern Med 1997;126:174).

7. Brenner BG, Roger M, Routy JP, Moisi D, Ntemgwa M, Matte C, et al. High rates of forward transmission events after acute/early HIV-1 infection. J Infect Dis 2007;195:951-9.

8. Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, et al. Probability of HIV-1 transmission per-coital act in monogamous heterosexual, HIV-discordant couples in Rakai, Uganda. Lancet 2001:357:1149-53.

9. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, et al. Rates of HIV-1 transmission per-coital act, by stage of HIV-1 infection, in Rakai, Uganda. J infect Dis 2005;191:1403-9.

10. Pilcher CD, Eron JJ Jr, Vemazza PL, Battegay M, Harr T, Yerly S, et al. Sexual transmission during the incubation period of primary HIV infection. J Am Med Assoc 2001; 286:1713–4.

11. Pilcher CD, Tien HC, Eron JJ Jr, Vernazza PL, Leu SY, Stewart PW, et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. J Infect Dis 2004;189 (10):1785-92.

12. Mark G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. J AIDS 2005;39:446-53.

13. Kassutto S, Rosenberg ES. Primary HIV Type-1infection. Clin Infect Dis 2004;38:1447-53.

14. Lavreys L, Baeten JM, Chohan V, McClelland S, Hassan WM, Richardson BA, et al. Higher set point plasma viral load and more sever acute HIV Type 1 (HIV-) illness predict mortality among high-risk HIV-1 infected African women. Clin Infect Dis 2006;42:1333-9.

15. Malhotra U, Berrey MM, Huang Y, Markee J, Brown DJ, Ap S, et al. Effect of combination antiretroviral therapy on T-cell immunity in acute human immunodeficiency virus type 1 infection. J Infect Dis 2000; 181 (1):121-31.

16. Berrey MM, Schacker T, Collier AC, Shea T, Brodie SJ, Mayers D, et al. Treatment of primary human immunodeficiency virus type 1 infection with potent antiretroviral therapy reduces frequency of rapid progression to AIDS. J Infect Dis 2001;183 (10):1466-75.

17. Oxenius A, Price DA, Easterbrook PJ, O'Callaghan CA, Kelleher AD, Whelan JA et-al. Early highly active antiretroviral therapy for acute HIV-1 infection preserves immune function of CD8+ and CD4+ T lymphocytes. Proc Natl Acad Sci USA 2000;97 (7);3382-7.

18. Lacabaratz-Porret C, Urrutia A, Doisne JM, Goujard C, Deveau C, Dalod M, Meyer L et al. Impact of antiretroviral therapy and` changes in virus load on human immunodeficiency (HIV)-specific T cell responses in primary HIV infection. J infect Dis 2003;187(5):748-57.

19. Hecht FM, Wang L, Collier A, Little S, Markowitz M, Margolick J, et al. A multicenter observational study of the potential benefits intiating combination antiretroviral therapy during acute HIV infection. J Infect Dis 2006;194:725-33.

20. MacNeal RJ, Dinulos JGH. Acute retroviral syndrome. Dermatol Clin 2006;24:431-8.

21. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection [review]. N Engl J Med 1998;339:33–9.

22. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med 1996;125:257–64 (erratum: Ann Intern Med 1997; 126:174).

23. Lyles RH, Muñoz A, Yamashita TE, Bazmi H, Detels R, Rinaldo CR, et al. Natural history of human immunodeficiency virus type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. J Infect Dis 2000;181:872–80.

24. Tattevin P, Camus C, Arvieux C, Ruffault A and`Michelet C. Multiple organ failure during primary HIV infection. Clin Infect Dis 2007;44:e28-29.

25. Busch MP, Satten GA. Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure [review]. Am J Med 1997;102:117–24 (discussion: 125–6).

26. Cabié A, Abel S, Lafaye JM, Béra O, Césaire R, Sobesky G. Dengue or acute retroviral syndrome? Presse Med 2000;29(21):1173-4.

27. Brook MG, Barnes A, Cook GC, Mabey DCA.Typhus-like illness caused by acute HIV seroconversion. Postgrad Med J 1991;67 (783):92-3.

28. Roth WW, Levett PN, Hudson CP, Roach TC, Womack C, Bond VC. HIV type 1 envelope sequences from seroconverting patients in Barbados. AIDS Res Hum Retroviruses 1997;13(16):1443-6.

29. Malavige GN, Fernando S, Fernando DJ, Seneviratne SL. Dengue viral infections. Post Grad Med 2004;80:588-601.

# 3 HIV-related respiratory conditions

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The respiratory system is one of the most common sites for problems in patients with human immunodeficiency virus (HIV), usually occurring later in the chronology of the disease. Accurate diagnosis and confirmation of infections or disease processes in the lung could provide a reason for offering HIV testing.

Respiratory diseases are one of the common problems associated with HIV infection. Patients may complain of cough, chest pain and difficulty breathing. Fever may or may not be present. The challenge to the health care provider is knowing when to suspect that the pulmonary condition is related to an underlying HIV infection. The possibility of HIV infection should be strongly considered when the pulmonary symptoms are accompanied by manifestations such as oral thrush, oral hairy leukoplakia, progressive or significant weight loss, alopecia, skin discoloration and pruritic papular eruption. Unusual infections, atypical presentation of common infections or severe disease should also point to a possible immune deficiency and hence should also warrant investigations for HIV. Multiple disease processes may affect the respiratory system in HIV infection and multiple pathological processes may occur simultaneously, especially in advanced immunodeficiency. This chapter outlines a few of the more common presentations.

## Sinusitis

Sinusitis commonly occurs in patients with HIV infection with a significantly higher occurrence of severe pathological changes in patients with acquired immunodeficiency syndrome (AIDS) compared with those with HIV infection without AIDS.[1] Patients commonly complain of fever, headache, nasal congestion and facial tenderness.

However, with CD4 cell counts below 200 cells/μL, symptoms and signs may be non-specific or absent while the disease itself could be more severe, often involves multiple sinuses, responds incompletely to antibiotic therapy, and can become chronic.[2] When patients do not respond to antibiotics targeted at common pathogens such as *Streptococcus pneumonia, Viridans streptococcus,* and *Haemophilus influenzae, Pseudomonas aeruginosa* should be considered. Although *P. aeruginosa* rarely causes sinusitis in individuals without HIV infection, it may account for 16-18% of cases of sinusitis in individuals with HIV infection and is associated with a high rate of recurrent disease. When the CD4 count is below 150 cells/μL, fungal pathogens such as *Aspergillus* should also be considered.[3]

## Tuberculosis

For many patients in the Asian and Pacific regions, infection with *Mycobacterium tuberculosis* is the first sign of an underlying HIV infection. Unlike most other opportunistic infections complicating HIV, tuberculosis may occur at any point during the course of HIV disease. *M. tuberculosis* infection may present with pulmonary or extrapulmonary disease. In early immunodeficiency, the patient may present with a fever and cough of more than one week's duration. A chest radiograph may show haziness of the upper lobes with or without cavitation.

Acid fast bacilli (AFB) (Figure 3.1) may be present in the sputum in 40-60% of cases. In some cases, particularly in areas with high prevalence of tuberculosis, patients may present with symptoms suggestive of acute bacterial pneumonia,[1] such as acute onset of high fever, chest pain and cough.

Chest x-ray may show consolidation with or without effusion in the middle or lower lung lobes. Persistence of fever after adequate treatment with antibacterial therapy should raise the suspicion of possible tuberculosis.

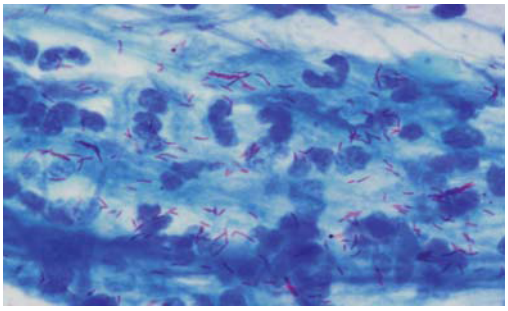

**Figure 3.1:** Acid fast bacilli stain of sputum

In patients with CD4 counts of less than 200 cells/μL, mediastinal lymphadenopathy and non-cavitary disease are more common. Chest x-rays may show haziness of the middle or lower lung areas or diffuse infiltrates without cavitation. Chest x-rays may be normal in 8-20% of cases.[4] In general, the AFB smear test becomes less sensitive in patients with advanced immunosuppression. Extra-pulmonary involvement, such as cervical lymphadenitis, pleural effusion, intra-abdominal tuberculosis, meningitis and disseminated infection occurs more frequently compared to patients without HIV.[5]

The diagnosis of tuberculosis in patients with HIV is often difficult and a differential diagnosis should include other infections such as pneumocystis pneumonia and severe bacterial pneumonia. Fever, weight loss and enlarged lymph nodes are also seen in patients with lymphoma. Lymph node biopsy is helpful in distinguishing tuberculosis from other diagnoses such as lymphoma, especially when the chest x-ray is normal or atypical of tuberculosis and the sputum is negative for AFB.

For patients with HIV infection, the diagnosis of tuberculosis can be made in the usual way: chest x-ray, sputum microscopy and culture, and histological examination and culture of tissue. These diagnostic methods have limited sensitivity.Newer tests that can shorten the time to diagnosis are already in clinical use or in various stages of clinical trials; tests include liquid-based rapid mycobacterial culture methods (BACTEC), mycobacteriophage–based diagnostic assays and nucleic acid based amplification tests.[6]

Once the diagnosis has been established, standard treatment protocols are available in most countries. Adherence to treatment should be emphasised since nonadherence is the most important factor for the emergence of drug resistant tuberculosis. If directly observed therapy (DOT) is not feasible, the next best option is to supervise treatment as closely as possible.[7] All patients with tuberculosis should be assessed for HIV risk factors, counselled and offered voluntary testing for HIV.

**Case study 3.1**

A 38-year-old man presented with intermittent fever and productive cough for more than a week. At presentation, his temperature was 38.7°C and he was not in respiratory distress. Breath sounds were decreased in the right lower lung field with dullness on percussion and increased tactile and vocal fremitus. A chest x-ray showed haziness of the right lower lung and infiltrates in the left lower lung region (Figure 3.2).

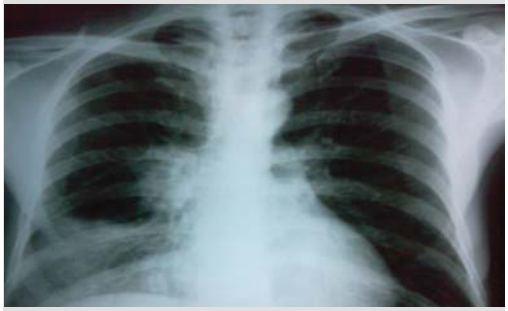

**Figure 3.2:** Right hilar fullness, increased opacity of the right lower lung and streaky density in the left base of the left lung.

Sputum microscopy showed Gram-positive cocci in pairs but was also positive for AFB. In individuals with HIV, tuberculosis may have an atypical presentation on chest x-ray. It is also possible that an acute bacterial infection could develop on top of a chronic infection. In areas where tuberculosis is endemic, screening for tuberculosis should be routinely done in patients presenting with possible pulmonary infection. Furthermore, HIV testing should be offered to patients with tuberculosis.

## *Pneumocystis jirovecii* pneumonia

*Pneumocystis jirovecii* pneumonia, formerly known as *Pneumocystis carinii* pneumonia (PCP), is one of the most common opportunistic infections affecting the lungs of patients with AIDS. It usually does not develop until the CD4 falls below 200 cells/μL.[8] The symptoms are insidious, including fever, non-productive cough and progressive or severe difficulty in breathing. Physical signs are frequently absent. Chest x-ray may be normal or with mild infiltrates in early disease.[9] Diffuse interstitial infiltrates, classically described as being of ground glass appearance, or a pulmonary oedema-like picture may occur in severe cases.[10]

Other AIDS-related conditions such as oral thrush may be present, which should immediately alert the health care worker for possible underlying HIV infection. Diagnosis is most often clinical but may be confirmed by demonstrating the *P. jirovecii* cyst from induced sputum or bronchoalveolar lavage.

The differential diagnosis includes other chronic infections such as tuberculosis and fungal infections. In patients not responding to a week or two of appropriate therapy, bronchoscopy should be considered, and empirical therapy for possible tuberculosis may be warranted in areas with high tuberculosis endemicity. All patients with the diagnosis of PCP must be offered voluntary counselling and testing.

**Case study 3.2**

A 32-year-old man who was previously treated for pulmonary tuberculosis four years ago presented with low grade fever and an unproductive cough for more than two weeks associated with progressive shortness of breath. The respiratory rate at presentation was 37 breaths/minute. On auscultation, there were harsh breath sounds. Further history revealed an episode of mild oral thrush a month previously and he claimed that he had lost about 5% of his body weight over the past six months. Chest x-ray revealed accentuated interstitial lung markings with infiltrates seen in the right upper lobe associated with apical pleural thickening (Figure 3.3).

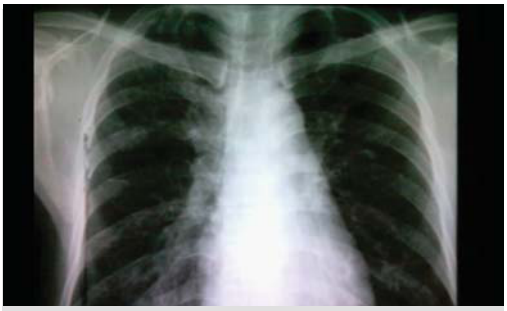

**Figure 3.3:** Prominent interstitial markings with fibrotic lesions in the apices

Sputum induction persistently failed to produce an adequate specimen for AFB testing. HIV infection was confirmed. He was treated for presumptive *P. jirovecii* pneumonia and discharged after eight days. Except for the persistence of the apical fibrotic changes, subsequent chest radiographs were clear.

Although the possibility of chronic infection, especially tuberculosis, should also investigated in this case, the progressive and severe difficulty in breathing with relative paucity of physical and chest x-ray findings are more characteristic of *P. jirovecii* pneumonia. The history of oral thrush further points to a possible HIV infection.

## Community-acquired pneumonia

Bacterial pneumonia frequently occurs in individuals with HIV infection and may be caused by common community acquired pathogens such as *Streptococcus pneumoniae.*[11,12] The symptoms of high fever and productive cough generally develop acutely within three days. Chest x-ray may show consolidation with or without pleural effusion. In individuals with HIV infection, acute bacterial pneumonia can develop at any CD4 level. During the early stages of HIV infection, concomitant HIV infection might be missed because the clinical presentation and treatment outcome are similar to that of individuals without HIV infection.

However, as immune function deteriorates, episodes of acute bacterial pneumonia may become more frequent and the clinical presentation may be more severe. Hence, in an individual with no other underlying comorbidities (e.g. advanced age, chronic obstructive pulmonary disease or diabetes mellitus), recurrent acute bacterial pneumonia (at least two episodes within 12 months) or severe presentations should raise the possibility of an underlying HIV infection.

## Penicilliosis

Penicilliosis is a disseminated infection caused by a fungus, *Penicillium marneffei*. The fungus is endemic in South East Asia and southern China. It rarely causes symptomatic infection in immunocompetent persons. In HIV disease, it may occur when the CD4 cell count falls below 100 cells/μL. Most patients present with fever, weight loss, enlarged lymph nodes and liver and skin lesions consisting of papules with central umbilication.[13,14] Up to one third of patients have cough and pulmonary symptoms. Chest x-ray findings may show diffuse reticulonodular, diffuse reticular, localised alveolar, localised reticular infiltration or cavitary lesions.[15] Health care workers should have a high index of suspicion for possible penicilliosis when faced with a patient coming from an endemic area presenting with the above signs and symptoms. Furthermore, since this disease develops during severe immunodeficiency, the presence of other conditions such as oral candidiasis could be a trigger for the diagnosis of HIV.

Diagnosis is confirmed by fungal culture or histopathology of specimens obtained from sites such as blood, skin, bone marrow, lymph node and liver.

## Lymphocytic interstitial pneumonitis

This condition is predominantly seen in children with HIV infection and is rare in adults. It may be difficult to differentiate from pulmonary or miliary tuberculosis in terms of symptoms (cough, difficulty of breathing and enlarged lymph nodes) and chest x-ray findings of diffuse reticulonodular patterns and enlarged hilar or mediastinal lymph nodes.[16]

The presence of parotid gland enlargement and clubbing of the fingers in some cases increases the likelihood of the diagnosis of lymphocytic interstitial pneumonitis. Diagnosis is usually clinical.

## Malignancies

Malignancies such as Kaposi's sarcoma, non-Hodgkin's lymphoma and lung carcinoma can also affect the respiratory system, but only Kaposi's sarcoma is discussed here.

### Kaposi's sarcoma

Kaposi's sarcoma affecting the lungs may occur with or without dermatological involvement. It may present with lobar consolidation similar to bacterial pneumonia or with mediastinal or hilar nodular lesions resembling tuberculosis or lymphoma. Non-resolution of these lesions after appropriate antibacterial or anti-tuberculosis therapy should raise the suspicion of a non-infectious mass lesion. Diagnosis is confirmed by biopsy. Pulmonary Kaposi's sarcoma remains an ominous diagnosis even in the era of combination antiretroviral therapy.[17]

**Case study 3.3**

A 43-year-old man presented with a 5-day history of fever and cough. Physical examination showed decreased breath sounds in the right lung base. Chest x-ray showed consolidation of the right lower lobe. He was started on antibacterial therapy and was discharged after three days. Four weeks later the patient was re-admitted for the same complaint. Repeat chest x-ray showed the same right lower lung finding. A diagnostic bronchoscopy was performed which showed pulmonary Kaposi's sarcoma. The patient had no skin lesions characteristic of Kaposi's sarcoma.

In this situation, an apparently otherwise healthy 43-year-old man not known to have HIV infection and with no warning signs presents with what seems to be a straightforward pneumonia. The lesson is to suspect HIV and conduct further investigations if presumptive pneumonia does not resolve as expected.

# References


1. Tarp B, Fiirgaard B, Møller J. The occurrence of sinusitis in HIV-infected patients with fever. Rhinology 2001;39(3):136-4.

2. Jung AC, Paauw DS. Diagnosing HIV-related disease using the CD4 count as a guide. J Gen Intern Med 1998;13(2):131-6.

3. Shah AR, Hairston JA, Tami TA. Sinusitis in HIV: microbiology and therapy. Curr Infect Dis Rep 2005;7(3):165-9.

4. Nyamande K, Lalloo UG, John M. TB presenting as community-acquired pneumonia in a setting of high TB incidence and high HIV prevalence. Int J Tuberc Lung Dis 2007;11(12):1308-13.

5. Harries AD. Tuberculosis and human immunodeficiency virus infection in developing countries. Lancet 1990;335(8686):387-90.

6. Furin J, Johnson J. Recent advances in the diagnosis and management of tuberculosis. Curr Opin Pulm Med 2005;11(3):189-94.

   Available at:
   http://cme.medscape.com/viewarticle/508659 (Cited on 20 April 2009).

7. World Health Organization. TB/HIV Clinical Manual. Second edition. Geneva, 2004 (WHO/HTM/TB/2004.329).

8. Wallace JM, Hansen NI, Lavange L, Glassroth J, Browdy BL, Rosen MJ, et al for the Pulmonary Complications of HIV Infection Study Group. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Am J Respir Crit Care Med 1997;155(1):72-80.

9. Gruden JF, Huang L, Turner J, Webb WR, Merrifield C, Stansell JD, et al.High-resolution CT in the evaluation of clinically suspected *Pneumocystis carinii* pneumonia in AIDS patients with normal, equivocal, or nonspecific radiographic findings. AJR Am J Roentgenol 1997;169(4):967-75.

10. DeLorenzo LJ, Huang CT, Maguire GP, Stone DJ. Roentgenographic patterns of *Pneumocystis carinii* pneumonia in 104 patients with AIDS. Chest 1987;91(3):323-7.

11. Koulla-Shiro S, Kuaban C, Bekec L . Caute community-acquired bacterial pneumonia in human immunodeficiency virus (HIV) infected and non-HIV infected adults in Cameroon: aetiology and outcome. Tuber Lung Dis 1996;77(1):47-51.

12. Magnenat JL, Nocod LP, Auckenthaler R, Junod AF. Mode of presentation and diagnosis of bacterial pneumonia in human immunodeficiency virus-infected patients. Am Rev Respir Dis 1991;144(4):917-22.

13. Sirisanthana T, Supparatpinyo K Epidemiology and management of penicilliosis in human immunodeficiency virus-infected patients. Int J Infect Dis 1998;3(1):48-53.

14. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated *Penicillium marneffei* infection in southeast Asia. Lancet 1994;344(8915):110-3.

15. Deesomchok A, Tanprawate S. A 12-case series of *Penicillium marneffei* pneumonia. J Med Assoc Thai 2006;89(4):441-7.

16. Zar HJ. Chronic lung disease in human immunodeficiency virus (HIV) infected children. Pediatr Pulmonol 2008;43(1):1-10.

17. Palmieri C, Dhillon T, Thirlwell C. Pulmonary Kaposi's sarcoma in the era of highly active antiretro viral therapy. HIV Med 2006;7(5):291-3.

# 4 HIV-related neurological conditions

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Health care workers should consider underlying human immunodeficiency virus (HIV) infection in patients who present with unexplained neurological illnesses especially opportunistic infections of the central nervous system (CNS), dementia and peripheral nerve disease.

## Introduction

Neurological conditions are common in patients with advanced, untreated HIV disease in the Asian and Pacific regions and have high morbidity and mortality rates. A recent study of hospital inpatients with HIV infection within seven countries of the Asian and Pacific regions reported that 43% of all inpatients were admitted with a neurological diagnosis and the most common diagnoses were opportunistic infections of the CNS.[1]

Similarly, in a study of 650 outpatients with HIV infection across the Asian and Pacific regions, 20% were found to have symptomatic sensory peripheral neuropathy, 12% had moderate-severe HIV-associated neurocognitive impairment and over 30% were diagnosed with depression.[2] This chapter provides suggestions for when a health care worker should consider underlying HIV infection in patients in the presence of a neurological disorder.

## Patients with undiagnosed HIV infection

During HIV seroconversion and early HIV infection, headache is probably the most common neurological symptom (Table 4.1). Patients, however, may also present with unique neurological illnesses such as aseptic meningitis, recurrent Guillain-Barré syndrome, isolated bilateral Bell's palsy, new onset seizures, distal symmetrical sensory peripheral neuropathy and myelopathy (spasticity of limbs, gait disturbance and bladder and bowel dysfunction).

Conditions indicating advanced HIV infection include: cryptococcal meningitis, tuberculous meningitis, progressive multifocal leukoencephalopathy (PML), cerebral toxoplasmosis, or primary CNS lymphoma. HIV-1-associated dementia (HAD) should also be considered in adults, especially young adults presenting with cognitive and behavioural change and psychomotor slowing. These diagnoses should prompt the health care worker to consider underlying HIV infection and offer testing as appropriate.

**Table 4.1: Neurological signs, symptoms and conditions related to HIV infection by CD4 cells count categorisation.**

| Seroconversion and early HIV infection (CD4 cell count > 500 cells/µL) | Intermediate HIV infection (CD4 cell count > 200 - < 500 cells/µL) | Advanced HIV infection (CD4 cell count < 200 cells/µL) |
|---|---|---|
| • Headache<br>• Aseptic meningitis<br>• Meningo-encephalitis<br>• Peripheral neuropathy<br>• Radiculopathy<br>• Brachial neuritis<br>• Guillain-Barré syndrome | • Guillain- Barré syndrome<br>• Chronic demyelinating neuropathy<br>• Polymyositis<br>• Bell's palsy<br>• Tuberculosis meningitis<br>• PML | • HIV-1 associated dementia<br>• Cerebral toxoplasmosis<br>• Cryptococcal meningitis<br>• Tuberculosis meningitis<br>• PML<br>• *Nocardia* brain abscess<br>• Primary CNS lymphoma<br>• CMV retinitis/encephalitis<br>• Transient ischaemic attack<br>• Stroke<br>• Painful sensory neuropathy<br>• Mononeuritis multiplex<br>• Autonomic neuropathy<br>• CNS vasculitis<br>• Herpes zoster encephalitis<br>• Hypomania<br>• Myelopathy |

PML: progressive multifocal leukoencephalopathy
CNS: central nervous system
CMV: cytomegalovirus

## Patients with established HIV infection

When patients with HIV infection present with neurological illnesses (headache, drowsiness, confusion, focal neurological lesions, dementia, neurocognitive impairment or painful sensory neuropathy), an assessment of their CD4 cell counts is critical.

In patients with a CD4 cell count above 200 cells/µL, CNS opportunistic infections are very uncommon, with the exception of PML and tuberculous meningitis, both of which can occur at higher CD4 cell counts.

Those with a CD4 cell count below 200 cells/µL are at increased risk of opportunistic diseases of the CNS, HAD and symptomatic distal symmetrical sensory peripheral neuropathy (Table 4.1).

HAD occurs in approximately 20% of patients with untreated HIV infection and CD4 cell counts less than 200 cells/µL.[3] Patients present with a 3-6 month history of cognitive and behavioural disturbance including poor concentration, forgetfulness and personality changes. Quite often these changes are most obvious to the patients' spouses, friends or partners. In addition, patients may have psychomotor slowing that manifests as clumsiness, unsteady gait, slowing of speech and impaired fine motor movements.[4]

The diagnosis of HAD is established by excluding other illnesses that may present in a similar fashion, including clinical depression. Hence, investigations should include a general workup that includes brain neuro-imaging to exclude other opportunistic disorders of the CNS, syphilis serology and thyroid function tests. Treatment with combination antiretroviral therapy (cART) using antiretrovirals that have good cerebrospinal fluid (CSF) penetration should be initiated[5] and is effective in reducing the symptoms of dementia in over 50% of patients.[6]

Improvement can be observed as early as four weeks after commencement of cART and continues for up to and beyond 18 months.[7]

In the Asian and Pacific regions, cryptococcal meningitis, cerebral toxoplasmosis and tuberculous meningitis are the most common opportunistic infections of the CNS diagnosed in inpatients with HIV infection.[1] Detailed descriptions of the clinical findings and investigations for these three opportunistic infections of the CNS are presented in Table 4.2.

**Table 4.2: Clinical features and investigations of cryptococcal meningitis, cerebral toxoplasmosis and tuberculous meningitis in patients with HIV infection***

| CNS opportunistic infection | Details |
|---|---|
| **Cryptococcal meningitis** | **Symptoms**<br>• Headache<br>• Fever<br>• Drowsiness<br>• Visual disturbance<br>• Stiff neck *(may not be present)*<br><br>**Signs**<br>• Obtundation<br>• Neck stiffness *(may not be present)*<br>• Photophobia<br>• Papilloedema[8] (rare)<br>• Cranial nerve palsies<br>• Signs of involvement of other organs (e.g. lung, heart)<br><br>**Investigations/results**<br>Serum cryptococcal antigen test<br>• Sensitivity > 90%<br>• Negative, then consider other causes of meningitis<br>• Positive, order CT or MRI of brain, then do lumbar puncture if no mass lesion<br><br>CSF<br>• CSF India ink test (70-90% positive), and/or<br>• Cryptococcal antigen test,<br>• CSF white cell count (usually < 20/mm$^3$)<br>• CSF glucose (normal or low) and<br>• CSF culture |

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**Table 4.2: Clinical features and investigations of cryptococcal meningitis, cerebral toxoplasmosis and tuberculous meningitis in patients with HIV infection*** (Continued)

| CNS opportunistic infection | Details |
|---|---|
| **Toxoplasma encephalitis** | **Symptoms**<br>• Headache<br>• Fever<br>• Confusion<br>• +/- Seizures<br>• Speech disturbance<br><br>**Signs**<br>• Cerebellar dysfunction<br>• Cranial nerve abnormalities<br>• Movement disorder<br>• Sensory disturbances<br>• Visual field defects<br><br>**Investigations/results**<br>Toxoplasma IgG antibody test<br>• Positive, but may be negative in up to 15% of patients<br><br>CT scan or MRI scan<br>• Multiple lesions<br>• Basal ganglia and corticomedullary junction often involved<br>• Ring-enhancing appearance<br>• Associated oedema<br><br>***Miscellaneous***<br><br>• CSF analysis NOT usually performed<br>• Functional MRI can be used to distinguish toxoplasma encephalitis from cerebral lymphoma<br>• Toxoplasma IgG seropositivity varies according to country |
| **Tuberculous meningitis** | **Symptoms**<br>• Fever<br>• Headache<br>• Altered sensorium<br><br>**Signs**<br>• Meningism<br>• Obtundation<br>• +/- Active pulmonary TB (seen in ~40% of cases) |

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**Table 4.2: Clinical features and investigations of cryptococcal meningitis, cerebral toxoplasmosis and tuberculous meningitis in patients with HIV infection* (Continued)**

| CNS opportunistic infection | Details |
|---|---|
| | **Investigations/results**<br>Chest X-ray<br><br>CT or MRI scan of brain<br>• Basal meningeal enhancement common<br>• May show tuberculoma also<br><br>CSF<br>• Measure CSF opening pressure<br>• Glucose<br>• AFB smear- 25% positive[9]<br>• AFB culture- 40% positive and sensitivity[9] |

RICP: raised intracranial pressure; CSF: cerebrospinal fluid; TB: tuberculosis; AFB: Acid fast bacilli
* There are a number of potential drug interactions that occur between various HIV antiretrovirals and treatment for the above listed CNS opportunistic infections.
Refer to http://www.druginteractions.org or http://www.hivclinic.ca

## Distal symmetrical sensory peripheral neuropathy

HIV may cause a painful distal symmetrical sensory peripheral neuropathy.[10] Patients present with aching, numbness, burning and tingling in the feet, ankles and calves. Rarely the upper thighs and hands may be involved.

Examination findings reveal a decrease in sensation, proprioception and vibration in the feet and diminished or absent ankle reflexes. Similar findings may sometimes be found more proximally. Other causes of peripheral neuropathy include use of other medications (e.g. isoniazid), diabetes and nutritional deficiencies.

**Case study 4.1**

A 34-year-old man presented with a two-week history of back pain, headache, neck stiffness, high fever, vomiting, weakness in both legs, difficulty with urination and defecation, and slowly progressive confusion.

His past history included an episode of pneumonia three months ago, the cause of which was not identified but which had been treated with ceftriaxone 2 gm per day.

- What is your differential diagnosis?
- What investigations would you consider necessary in clarifying the differential diagnosis?

An HIV antibody test was performed and was positive.

- What can you see in the patient's chest X-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI) brain and spinal cord, and sputum modified acid-fast bacilli stain (Figure 4.1)?

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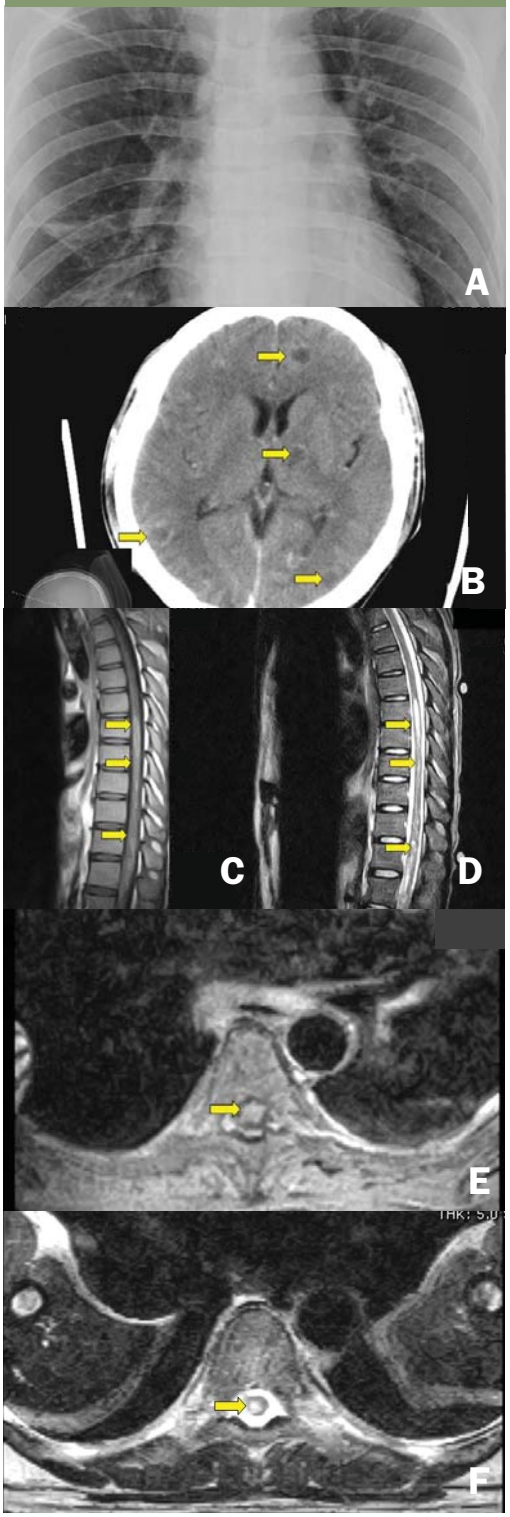
## Case study 4.1 (Continued)



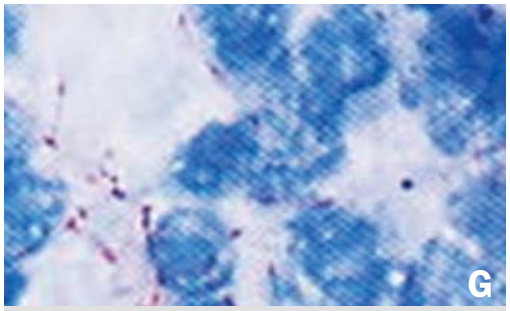




**Figure 4.1 A**: Chest X-ray showing pulmonary infiltration, **B**: CT scan showing a subcortical multiple small brain abscess, **C**, **D**, **E**, **F**: MRI spinal cord showing multiple intraspinal abscesses, **G**: Sputum modified acid fast bacilli stain was positive

MRI revealed spinal cord lesions and multiple brain abscesses. A lumbar puncture was performed. The opening/closing pressures were 29/20 $cmH^2O$ and the CSF was slightly turbid. CSF analysis revealed: WBC = 4.9 x $10^{11}$ cells/L, a lymphocytic predominance, CSF protein=144 mg/dL; CSF/Blood sugar 18/118 mg/dL; CSF Gram stain, Indian ink and acid-fast and modified acid-fast stains were negative. CSF culture was negative for aerobic bacteria; CSF toxoplasma antibody was negative; CSF PCR for cytomegalovirus (CMV) was negative. PCR for *Mycobacterium tuberculosis* was positive (IS6110 and Reg2-Reg3 gene detection).

- How would you manage this patient?

The patient began treatment with antituberculous drugs plus dexamethasone at 12 mg/day for 3 weeks, then tapered over the following 3 weeks plus intravenous co-trimoxazole for possible *Nocardia* infection, and he had improvement in his confusion and other symptoms. Two months after his diagnosis he had recovered except for some residual paraparesis.

**Comment**

Patients with very low CD4 cell counts who present with subacute headache, fever, drowsiness and confusion, neck stiffness and lung involvement may have *M. tuberculosis* infection. Infection with *Nocardia spp*. should also be considered.

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## Case study 4.1 (Continued)

The diagnosis of CNS disease is optimised by taking a thorough history and performing a careful clinical examination. In resource-limited settings, CT and MRI scans may not be available. Knowledge of the seroprevalence of toxoplasmosis in the region or the country is useful to gauge the likelihood of whether focal CNS lesions may be toxoplasmosis.

Further knowledge of the local epidemiology of tuberculosis and cryptococcal disease also assists in helping to diagnose opportunistic infections of the CNS. Patients who are toxoplasma antibody positive but who are receiving co-trimoxazole prophylaxis are much less likely to present with cerebral toxoplasmosis. Similarly, patients receiving fluconazole prophylaxis are less likely to present with disseminated cryptococcal disease and cryptococcal meningitis.

## Case study 4.2

A 40-year-old man with HIV infection presented with a one-day history of right side weakness, drowsiness, and aphasia. He did not have headache and was afebrile with no signs of lung infection and no neck stiffness. He was diagnosed with HIV nine years before and had been taking combination stavudine, lamivudine and nevirapine (GPO-vir) for 4 years; his CD4 cell count was 384 cells/μL. His past history included disseminated cryptococcosis and pulmonary tuberculosis. He had no hypertension, dyslipidaemia, or other stroke risk factors.

- What is your differential diagnosis?
- What investigations would you consider necessary in clarifying the differential diagnosis?
- What can you see in the CT scan and magnetic resonance angiogram (Figure 4.2)?

He was referred to a neurologist who confirmed the diagnosis of left middle cerebral artery occlusion. An echocardiogram, CSF examination and CSF-PCR for mycobacteria, herpes simplex virus, and herpes zoster virus were all negative.

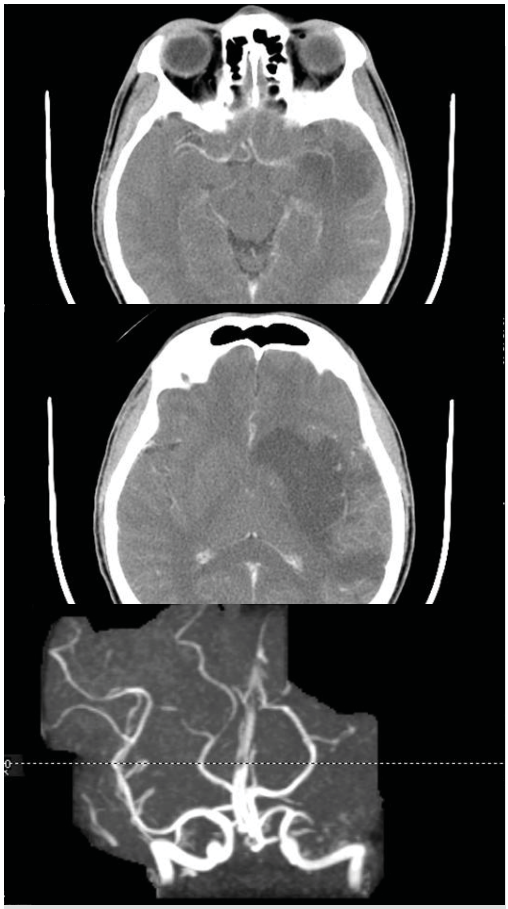

**Figure 4.2** CT brain scan showing hypodense lesion in left frontoparietal region and magnetic resonance angiogram showing occlusion of left middle cerebral artery.

- How would you manage this patient?

The patient began treatment with aspirin and rehabilitation including mobilisation and physiotherapy. Partial resolution of his right hemiparesis occurred after 6 months.

**Comment**

Although stroke is an uncommon neurological condition in HIV patients receiving cART, this patient had a stroke that left him with severe disability. Infectious diseases associated with stroke, such as varicella zoster virus and syphilis, are very difficult to rule out in resource-limited settings.

Continued over page

**Case study 4.2** (Continued)

However, in this case, the absence of clinical clues that would have indicated opportunistic infections of the CNS, such as fever, headache, neck stiffness and concurrent lung infection, helped the physician to minimise the diagnostic likelihood that this was an opportunistic infections of the CNS.

# Conclusions

Patients with undiagnosed HIV infection may present to the health care worker with various neurological signs and symptoms. Underlying HIV infection should be strongly considered in the differential diagnosis of CNS diseases including cryptococcal meningitis, cerebral toxoplasmosis, tuberculous meningitis, CNS lymphoma, unexplained symptomatic distal symmetrical sensory neuropathy, myelopathy. It should also be considered in young patients presenting with dementia.

## Acknowledgments

We thank Stephen D. Martin, Chiang Mai University; Luxshimi Lal and Edwina Wright from the Asia Pacific NeuroAIDS Consortium (APNAC) for assistance with the text; and APNAC members for APNAC data provided; and Chatchai Ekwitayawechnukul for the preparation of the case studies.

# References

1. Wright E J, Brew B J, Arayawichanont A, Samintharapanya K, Kongsaengdao S, Lal L, et al. High burden of neurological disease in HIV positive inpatients within the Asian and Pacific regions. Poster presentation. Abstract no. MOPEB078. In: The fourth International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; 2007 22-25 July; Sydney.

   Available at: http://www.ias2007.org/pag/Abstracts.aspx?SID=153&AID=1925 (Last accessed 15 September 2009).

2. Wright E, Brew B, Arayawichanont A, Robertson K, Samintharapanya K, Kongsaengdao S, et al. Neurologic disorders are prevalent in HIV-positive outpatients in the Asian and Pacific regions. Neurology 2008;71(1):50-6.

3. McArthur JC, Hoover DR, Bacellar H, Miller EN, Cohen BA, Becker JT, et al. Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. Neurology 1993;43(11):2245-52.

4. Brew BJ. HIV Neurology. New York: Oxford University Press, 2001.

5. Cysique LA, Maruff P, Brew BJ. Antiretroviral therapy in HIV infection: are neurologically active drugs important? Arch Neurol 2004;61(11):1699-704.

6. Tozzi V, Balestra P, Galgani S, Narciso P, Ferri F, Sebastiani G, et al. Positive and sustained effects of highly active antiretroviral therapy on HIV-1-associated neurocognitive impairment. AIDS 1999;13(14):1889-97.

7. Cohen RA, Boland R, Paul R, Tashima KT, Schoenbaum EE, Celentano DD, et al. Neurocognitive performance enhanced by highly active antiretroviral therapy in HIV-infected women. AIDS 2001;15(3):341-5.

8. Graybill JR, Sobel J, Saag M, van Der Horst C, Powderly W, Cloud G, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. Clin Infect Dis 2000;30(1):47-54.

9. Thwaites GE, Duc Bang N, Huy Dung N, Thi Quy H, Thi Tuong Oanh D, Thi Cam Thoa N, et al. The influence of HIV infection on clinical presentation, response to treatment, and outcome in adults with tuberculous meningitis. J Infect Dis 2005;192(12):2134-41.

10. Keswani SC, Pardo CA, Cherry CL, Hoke A, McArthur JC. HIV-associated sensory neuropathies. AIDS 2002;16:1-13.

# 5 HIV and sexually transmitted infections

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All patients with or at risk of sexually transmitted infections (STIs) must be offered appropriate STI and human immunodeficiency virus (HIV) testing. In addition, health care workers should initiate STI and HIV testing in settings where antenatal and gynaecological assessments are carried out.

## Introduction

STIs rank among the important causes of major public health problems in the Asian and Pacific regions.[1,2] STI and HIV infection facilitate each other's transmission and share many epidemiological determinants, and hence the control of STIs is an essential component in the control of HIV.[3]

The lack of adequate laboratory services in remote parts of the Asian and Pacific regions limits the ability of diagnosing and managing STIs appropriately according to international guidelines.[4] Screening for STIs and HIV is rarely offered in general outpatient clinics or wards in most of the hospitals in the region. Not all antenatal clinics offer routine STI and HIV screening either. Diagnosing STIs in children is difficult in most settings since health workers fail to consider sexual abuse risk or recognise symptoms in children.

Most people present to local health clinics where staff often have limited knowledge of STIs and thus often fail to recognise symptoms, make correct diagnoses or manage patients appropriately. Some people with STI symptoms may present late or in fact never attend health facilities because of personal shame and fear of discrimination, or because they do not consider the STI a significant health problem.

Increasing numbers of people are now presenting with secondary or tertiary complications of STIs and with symptomatic HIV infection, often at a late stage.[3,4,5]

## Where and when patients present

People with STIs may present in a variety of contexts such as traditional health settings, commercial pharmacies, private practices, or community-based health clinics. Apart from the specialised STI clinics, other health facilities rarely offer proper history-taking, examination, testing, counselling and screening of non-symptomatic STIs and HIV infection.

In addition, a number of people may be referred to STI clinics from blood banks and antenatal clinics if they are diagnosed with HIV, syphilis and hepatitis B or C during routine screening for counselling and management.

## Clinical symptoms and signs

Some patients may present syndromically (urethral or vaginal discharge, genital ulcerative disease, lower abdominal pain syndrome, scrotal swelling, or inguinal buboes). Some symptoms are self-limiting or may be considered trivial enough to be ignored. Most patients, however, are asymptomatic and may not be aware that they have an infection. The key to identifying patients at risk of infection is to take a sexual history.

## Taking a sexual history

Taking a proper sexual history can be challenging for both the health worker and the patient. However, a sexual history is imperative in making a proper diagnosis and effectively assisting in the management of patients and their partner(s). Building a good rapport with the patient is an essential component of any history taking. Full confidentiality in the information provided by the patient about examination findings and results of investigations and tests should be assured.

A sexual history should be taken in privacy without the presence of a third person (unless agreed by the patient). The provider also should ask permission from the patient before asking for any sensitive questions regarding his/her sexual history. Attention should be paid to what the patient is saying without being judgmental or showing shyness, shock or nervousness. Simple, non-medical language should be used whenever possible. The patient's decision not to answer any questions should be respected. Some of the specific relevant sexual health questions that can be asked as part of a complete sexual history are noted below:

| Specific sexual history |
|---|
| How old were you when you first had sex? |
| Do you have sex with men, women, or both? |
| Do you have regular/concurrent/ casual partners? |
| How many casual partners do you have? In the past month? In the past six months? Can these partners be contacted for treatment? |
| When was the last time you had sex? (If the patient is sexually active) |
| What form of sex was it: oral, anal or vaginal? |
| Insertive or receptive? |
| Did you use condoms? |
| How often do you use condoms? |
| Have you ever been compensated for sex with alcohol, drugs or other things? If yes, how often has this happened in the past month? In the past six months? |
| Have your sexual activities been related to alcohol or drug use? |
| Do you use drugs such as cannabis, speed and heroin? |
| Have you previously had an STI? When? What was it? Was it treated? Where and by whom? |
| Have you ever had an HIV test? When? Do you know the result? |
| Do you know how to use a condom? |
| Where do you get condoms from? |
| If you do not use condoms, what is the reason for not using them? |

## Examination

Privacy, gloves and a good light source are essential for the examination. The skin, mucous membranes (mouth and eyes) and lymph nodes should be examined prior to a genital examination, as infections such as syphilis and HIV can present with more general symptoms.

## Making a diagnosis

Where possible, an accurate diagnosis using routine tests such as wet preparations, gram staining, PCR, rapid tests and serology should be attempted. The lack of diagnostic microbiology and pathology laboratories, however, impels health workers to manage STIs using the WHO syndromic management approach, hence specific STIs are not always diagnosed and asymptomatic STIs remain largely undetected.

In addition, other conditions which may mimic STIs (e.g. ulcerative diseases) may present in the genital area. If these conditions do not respond to standard therapies, the patient should be referred on for further evaluation.

# STIs and HIV

HIV is a sexually transmitted infection and its transmission is strongly linked with the presence of other STIs, especially ulcerative STIs.[3,6]

Both symptomatic and asymptomatic STIs increase genital HIV viral load and STI treatment is associated with declines in viral loads thus reducing infectivity.

People at high risk (e.g. those with concurrent partners, STI symptoms, men having sex with other men, sex workers, intravenous drug users) and their sexual contacts, even when asymptomatic, should be offered full screening for STIs including serology for syphilis and hepatitis B and voluntary counselling and testing (VCT) for HIV.

However, HIV testing should not be compulsory and a patient's decision to refuse testing must be respected.

People with HIV infection with STIs may have a similar presentation as those without HIV. Unusual clinical presentations of conditions such as herpes, syphilis, molluscum contagiosum and warts may occur. However, detection of a new STI in a person with HIV must be carefully and tactfully assessed in order to initiate contact tracing and partner notification with due consideration of confidentiality for the initially identified person with HIV.

**Case study 5.1**

A 32-year-old woman presents to the STI clinic with vaginal discharge and painful sores around the vulva for two weeks.

What specific history would you take?

She is a sex worker and has had oral, anal and vaginal sex with and without condoms in the past. She has a history of previous STIs and was treated by a private practitioner. She has never had any blood tests for STIs or HIV. She frequently exchanges alcohol and drugs for sex. She has an intrauterine contraceptive device.

Examination revealed a cluster of red, vesicular lesions around the vulva and raised hard rimmed, painless ulcers on the vaginal wall with copious amounts of foul-smelling frothy discharge inside the vaginal vault. Her cervix was inflamed with mucopurulent discharge and bled when a cervical swab was taken.

A high vaginal swab was also taken for direct microscopy and culture.

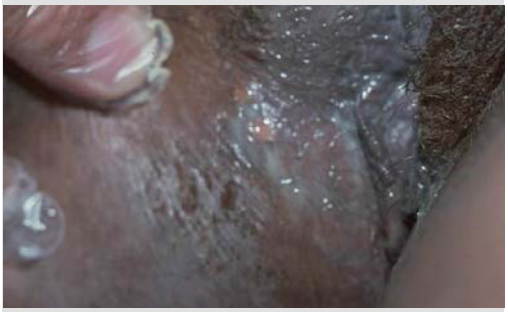

**Figure 5.1:** Vaginal discharge and sores

| The differential diagnosis includes |
|---|
| **Infections** |
| • Herpes/ syphilis/ donovanosis/LGV/ chancroid<br>• *E. Histolytica* |
| **Trauma** |
| • Mechanical/ chemical |
| **Allergic** |
| • Fixed Drug Eruptions (doxycycline)/ generalised reactions (Fansidar/ Cotrimoxazole) |
| **Neoplastic** |
| • Premalignant/ malignant conditions |
| **Secondary** |
| • Infestations (scabies/ pubic lice)/ dermatosis |
| **Others** |
| • Bechets, pemphigoid/pemphigus/ Crohn's Reiters, lichen planus |

Continued over page

**Case study 5.1** (Continued)

What tests are you able to conduct in your setting?

Ideally this woman should have a wet preparation and tests to detect chlamydia and gonorrhoea. Blood should be taken to test for syphilis, hepatitis B/C and she should be offered HIV (1 and 2) screening.

The laboratory results showed:

- Wet Prep: *Trichomonas vaginalis* and Bacterial Vaginosis
- Gram Stain: Gram negative intracellular diplococci; *Neisseria gonorrhoeae*
- Blood: Rapid plasma reagin (RPR) test for syphilis 1:32 *Treponema pallidum* haemagglutination assay (TPHA) to confirm syphilis: reactive
- Hepatitis BsAg: reactive
- HIV-1 reactive (confirmed by repeat test)

How will you manage this case now?
Standard treatments for the infections listed.
Cotrimoxazole 1 DS od until reviewed for HIV

What are some of the short- and long-term management plans for this patient?

# References


1. WHO Report, Antenatal Clinic STI Survey: Apia, Samoa July, 2000 WHO 3-6 Ministry of Health, Samoa, with support from the World Health Organization Regional Office for the Western Pacific, Manila, Antenatal Clinic STI Survey: Apia, Samoa: July 2000.

   Available at:
   http://www.wpro.who.int/NR/rdonlyres/31F4B939-F764-45E1-BEA9-C28DB1B567A4/0/AntenatalClinicSTISurvey_SMA_2000.pdf (Cited 15 June 2009)

2. Parker KA, Koumans EH, Hawkins RV, Massanga M, Somse P, Barker K, et al. Providing low-cost sexually transmitted diseases services in two semi-urban health centers in Central African Republic (CAR): characteristics of patients and patterns of health care-seeking behavior. Sex Transm Dis 1999;26(9):508-16.

3. Adler M, Cowen F, French P, Mitchell H, Richens J, editors. ABC of Sexually Transmitted Infections. Fifth Edition. BMJ Books: Blackwell Publishing, 2004.

4. Guidelines for HIV/AIDS, STI, and Behavioural Risk Factors Surveillance: Pacific Island Countries and Areas, World Health Organization Regional Office for the Western Pacific, 2000.

   Available at:
   http://www.wpro.who.int/NR/rdonlyres/4EEC1089-216F-4D6D-9C1C-54910DB6A14D/0/Guidelines_for_HIV_AIDS_STI_Behavioural_Risk_Factors_Surveillance_PIC_2000.pdf (Cited 15 June 2009).

5. Ngeow YF. STD and HIV epidemiology in Asia. International Conference on AIDS. Int Conf AIDS 1994;10:5 (Abstract no. PS7).

   Available at:
   http://gateway.nlm.nih.gov/MeetingAbstracts/ma?f=102209626.html
   (Cited 15 June 2009).

6. Plourde PJ, Pepin J, Agoki E, Ronald AR, Ombette J, Tyndall M, et al. Human immunodeficiency virus type 1 seroconversion in women with genital ulcers. J Infect Dis 1994; 170:313-7.

# 6 HIV-related oral and gastrointestinal conditions

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Gastrointestinal diseases are common manifestations in patients with human immunodeficiency virus (HIV). Oral diseases, dysphagia, odynophagia, diarrhoea, abdominal pain, jaundice and gastrointestinal bleeding may be the result of opportunistic infections.

Confirming the presence of these infections along with a sensitive history may indicate the need for HIV testing. The chronology of gastrointestinal conditions is illustrated below (Figure 6.1).

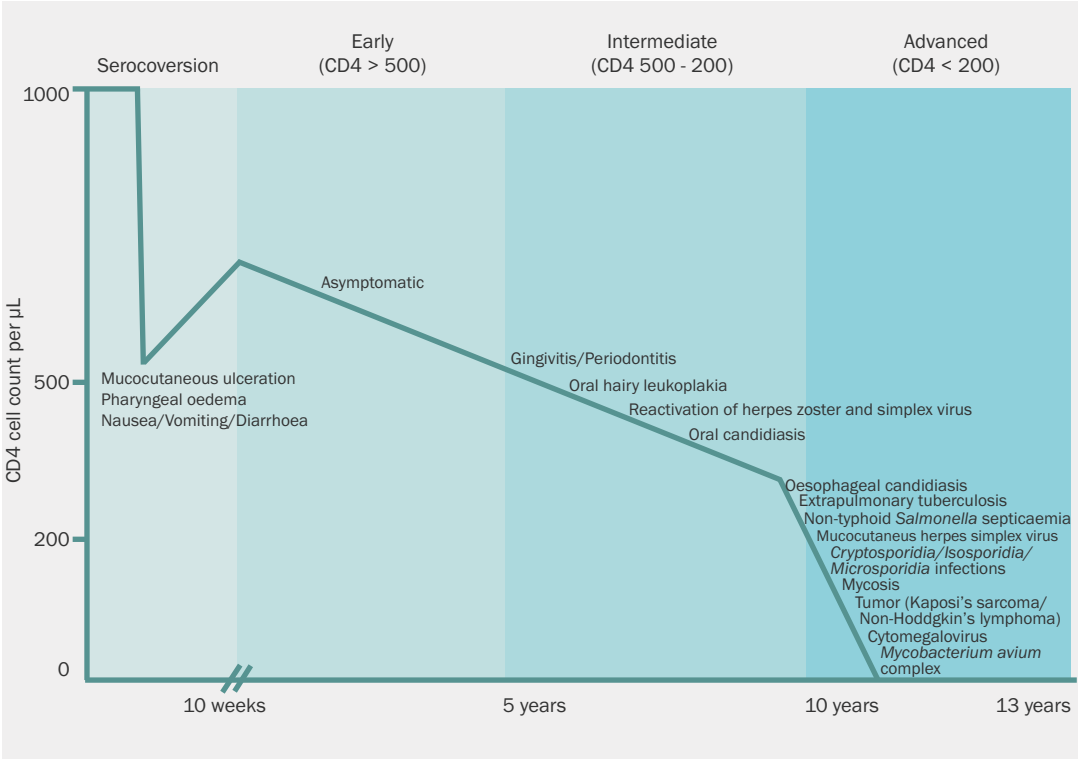


**Figure 6.1**: Chronology of the natural history of gastrointestinal manifestations of HIV infection correlated with CD4 cell count.

# Oral manifestations

A summary of the oral manifestations of HIV infection can be found in the table 6.1.

## Candidiasis

Oral candidiasis is a common opportunistic infection of the oral cavity caused by an overgrowth of *Candida* species, the commonest being *Candida albicans*. Oropharyngeal candidiasis can present in one of four forms:

**Pseudomembranous candidiasis** (commonly known as thrush); the diagnosis is fairly straightforward and the whitish plaque can generally be scraped off with a spatula (Figure 6.2).

**Erythematous candidiasis** appears as an atrophic, smooth depapillated area on the palate and dorsal tongue (Figure 6.3). Lesions appear red or erythematous.

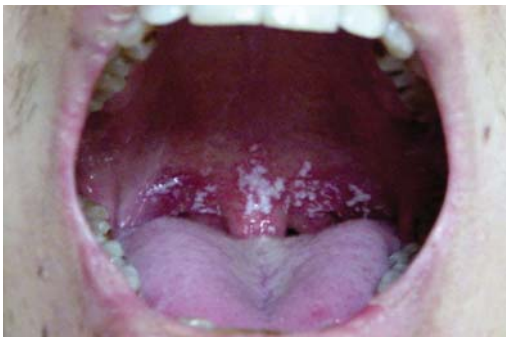

**Figure 6.2**: Pseudomembranous candidiasis

**Hyperplastic candidiasis** consists of non removable, speckled or homogenous white patches, lacking corrugations. The condition is rare and the diagnosis difficult to distinguish from oral leukoplakia (see below). Lesions should completely resolve with routine antifungal therapy.

**Angular cheilitis** presents as inflammation or fissuring in the corners of the mouth, which is often a mix of dermatitis due to irritation from saliva, *Candida* and sometimes bacterial infections.

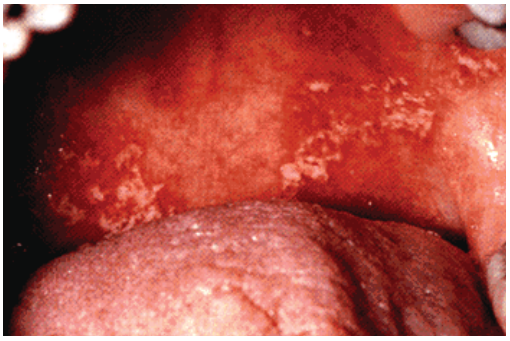

**Figure 6.3**: Erythematous candidiasis.

## HIV-related periodontal diseases

Gingivitis is common in people with HIV, although the rate has fallen in patients treated with combination antiretroviral therapy (cART). The most common forms, **linear gingival erythema** (Figure 6.4) and **necrotising ulcerative periodontitis** (Figure 6.5) appear to be unique to immunocompromised individuals. Linear gingival erythema appears as asymptomatic 1–3 mm erythematous bands along the gingival margin. This periodontal condition may go unnoticed until significant damage (i.e. teeth loss) has occurred.[1]

Necrotising ulcerative periodontitis is a more severe form of gum disease seen in immunodeficient patients with HIV, with ulceration extending into the underlying alveolar bone. It may be rapidly progressive and is usually associated with significant pain, making food difficult to eat. People with necrotising ulcerative periodontitis are typically severely immunodeficient with a mean CD4 cell count of 32 cells/μL.[2]

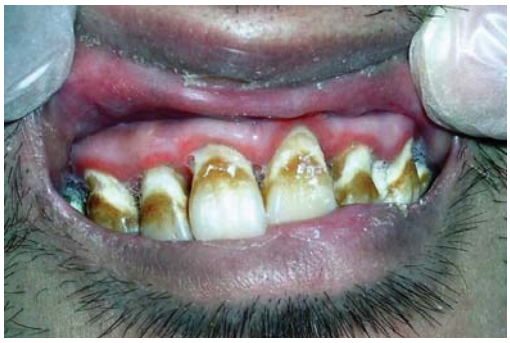

**Figure 6.4**: Linear gingival erythema

**Figure 6.5**: Necrotising ulcerative periodontitis

## Viral infections

Both herpes simplex virus and cytomegalovirus can cause extensive mucosal ulceration. Extensive and persistent non-healing mucosal ulceration should be an indication for considering HIV testing. Herpes lesions that persist for more than one month constitute an acquired immunodeficiency syndrome (AIDS)-defining illness.

Intra-oral varicella zoster infections may lead to bone necrosis and loss of teeth in the affected areas.

## Oral hairy leukoplakia

Oral hairy leukoplakia is common in people with untreated HIV infection. It is important to diagnose oral hairy leukoplakia because of its strong association with HIV and disease progression. It characteristically presents as asymptomatic, vertical, white, hyperkeratotic folds on the lateral margins of the tongue. Unlike thrush, it cannot be scraped off and does not improve with anti-fungal treatment (Figure 6.6).

Diagnosis is usually clinical but can be confirmed by biopsy, which demonstrate the presence of Epstein-Barr virus in basal epithelial cells. Oral hairy leukoplakia does not require specific treatment and rarely causes symptoms.

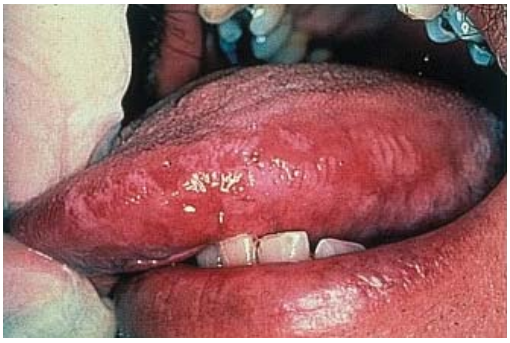

**Figure 6.6**: Oral hairy leukoplakia

Source: Foltyn P, Marriott D. Managing HIV. Part 5: Treating secondary outcomes. 5.2 HIV and oral disease. Med J Aust 1996;164(6):357-9.

## Human papillomavirus infection

Oral warts are a manifestation of human papillomavirus infection that has been infrequently noted in persons with HIV. Oral warts can occur anywhere within the oral cavity, either as single or multiple lesions. The appearance may be sessile, cauliflower, papular or macular. A recent study described an increased incidence of oral warts in HIV-seropositive patients in the era of combination antiretroviral therapy (cART) associated with reductions in virus load, which suggests that this may in part be related to immune reconstitution.[3]

## Kaposi's sarcoma

Kaposi's sarcoma appears typically as a violaceous macular or nodular lesion on the hard palate or gingiva and on the skin (Figures 6.7 and 6.8). The most common site for Kaposi's sarcoma is the skin, but other organ involvement including visceral organs, bone and lymph nodes may be seen. Diagnostic confusion may arise when evaluating the macular type or if the lesion infiltrates the gum. In these cases, biopsy may be appropriate. Differential diagnosis includes bacillary angiomatosis, non-Hodgkin's lymphoma, and cutaneous fungal or bacterial infections. Human herpes virus 8 has been identified as the causative agent of Kaposi's sarcoma.[4]

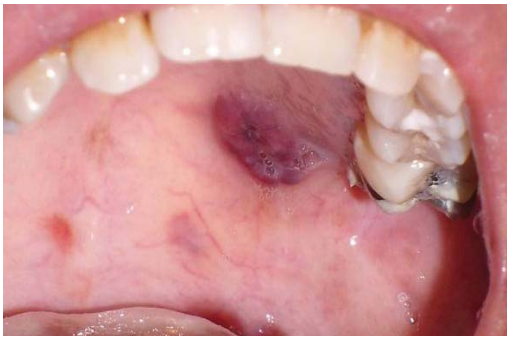

**Figure 6.7**: Oral Kaposi's sarcoma

Histologically, Kaposi's sarcoma appears as a spindle cell component with slit-like vascular spaces containing erythrocytes, and a variable inflammatory cell infiltrate. AIDS-associated Kaposi's sarcoma may occur in all HIV transmission groups but appears at a particularly high rate among men who have sex with men (MSM). Data from the Multistate AIDS-Cancer Match Registry showed a relative risk of 106 000-fold in MSM and 13 000-fold in people exposed to HIV through injection drug use or heterosexual activity, compared with the general population.[5]

The reason for such enormous relative risk is because the background rate of Kaposi's sarcoma is so low among general population. While the relative risk of Kaposi's sarcoma in homo/bisexual men is only 5 - to 10-fold higher than in other HIV-exposure groups.

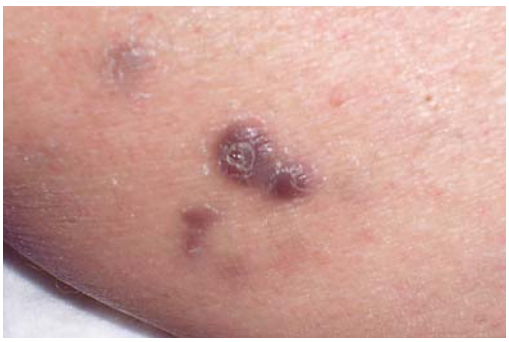

**Figure 6.8**: Cutaneous Kaposi's sarcoma

## Non-Hodgkin's lymphoma

Oral lymphoma is a rare manifestation of HIV-associated non-Hodgkin's lymphomas (NHL) which consist of a group of neoplasms that includes primary central nervous system lymphomas, systemic lymphomas, and primary effusion lymphomas. Oral NHL may present as a soft, rapidly enlarging mass or as ulcerative lesions which may be confused with aphthous ulcers (Figure 6.9). Biopsy is required for diagnosis.

**Figure 6.9**: B cell lymphoma on gingival margin of mandibular premolar teeth

Source: Foltyn P. HIV-related oral disease. In: Stewart G. Could it be HIV? 2nd edition. Sydney: Australasian Medical Publishing Company Limited, 1994:27.

## Oral aphthous ulceration

The lesions typically occur as multiple oval and shallow ulcers on the non-keratinised epithelium of the oral cavity (Figure 6.10). They can be extremely painful and can interfere with eating. Major aphthous ulcerations are associated with advanced HIV disease (CD4 cell counts below 50 cells/μL).[1] Biopsy may be required to clarify the differential diagnosis.

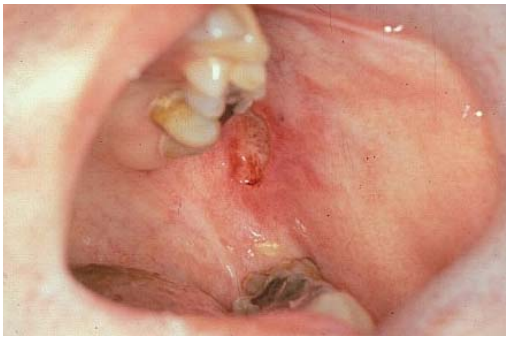

**Figure 6.10**: Cytomegalovirus oral ulcer of the cheek

Source: Foltyn P. HIV-related oral disease. In: Stewart G, editor. Could it be HIV? 2nd edition. Sydney: Australasian Medical Publishing Company Limited, 1994:27.

## Oesophageal manifestations

For patients who present with dysphagia alone, 54% will have *Candida* oesophagitis (Figure 6.11), whereas those with odynophagia may have cytomegalovirus ulcers or idiopathic ulcerations (Figure 6.12).[6,7]

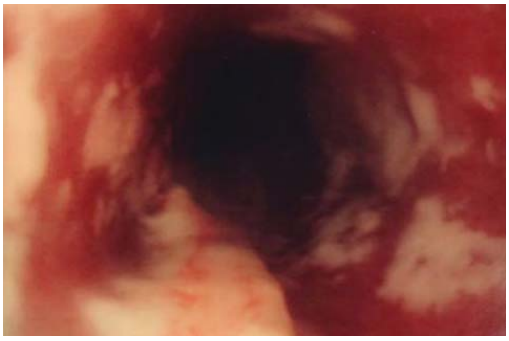

**Figure 6.11**: *Candida* oesophagitis

Oral candidiasis can be found in the majority (80%) of cases of *Candida* oesophagitis.[8] Patients with cytomegalovirus oesophagitis typically present with fever and focal oesophageal pain. Oral ulcers are found in only 38% patients with herpes simplex virus oesophagitis.[9]

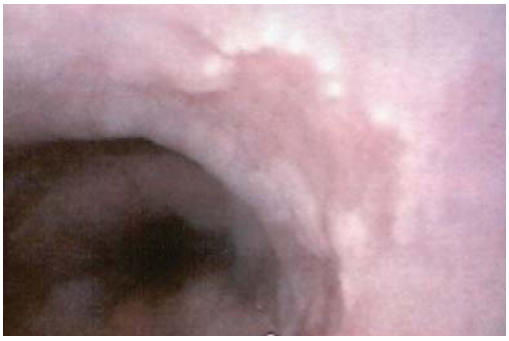

**Figure 6.12**: Cytomegalovirus oesophagitis

**Case study 6.1**

A 35-year-old man presented with a 4-week history of fever, dysphagia and odynophagia. He was diagnosed with HIV infection 6 months ago but he failed to continue medical follow-up. His current CD4 count was 11 cells/μL. As most patients (80%) with *Candida* esophagitis have oral candidiasis, he was empirically treated with fluconazole.

The symptoms remained unchanged after seven days. Upper endoscopy revealed oesophageal candidiasis. Fungal culture, which showed *C. krusei*, was found to be resistant to fluconazole. He was successfully treated with itraconazole.

**Summary:** This case illustrates how resistant organisms can confuse a diagnosis especially when the disease is treated empirically. Clinical improvement of *Candida* oesophagitis usually occurs within the first week of therapy. However, treatment failure may result from the emergence of drug resistance or be due to other causes of odynophagia such as cytomegalovirus oesophagitis.

Risk factors for resistance include advanced immunosuppression, non-albicans *Candida* species and chronic exposure to azole therapy. Upper endoscopy is indicated in patients with odynophagia who have failed to respond to empirical antifungal therapy.

**Table 6.1: Oral manifestations**

| Clinical signs | Aetiology | Associated features | CD4 count (cells/µL) at risk |
|---|---|---|---|
| **Oropharyngeal candidiasis** | *Candida* spp. | Whitish plaque easily removed with spatula | < 200 |
| **Gingivitis and periodontitis** | Bacterial plaques | - Linear gingival erythema<br>- Necrotising ulcerative gingivitis, periodontitis, stomatitis | < 400 |
| **Mucosal ulcerations** | Aphthous ulceration | | Any (< 50 for major ulcerations) |
| | HSV | | < 300 |
| | CMV | | < 100 |
| **Oral hairy leukoplakia** | EBV | - Rare in cART era<br>- MSM<br>- Asymptomatic whitish folds on lateral margins of tongue<br>- Cannot be scraped off | < 200 |
| **Kaposi's sarcoma** | HHV-8 | Violaceous macular or nodular lesion on hard palate or gingiva | < 100 |
| **Non-Hodgkin's lymphoma** | | Soft, tumour-like, rapidly enlarging mass | < 100 |

HSV: herpes simplex virus
CMV: cytomegalovirus
EBV: Epstein-Barr virus
HHV-8: human herpes virus type 8
MSM: men who have sex with men
cART: combination antiretroviral therapy

# Gastrointestinal manifestations

## Diarrhoea

*Shigella*, *Campylobacter* or entero-invasive *Escherichia coli* gastroenteritis are typical infections found in acute dysentery in patients with HIV disease. Infections such as *Campylobacter, Giardia* and *Entamoeba histolytica* may also be found. Chronic diarrhoea is associated with *Mycobacterium avium* complex (MAC), *Cryptosporidium*, *Giardia* or *Isospora* infections. Severe watery diarrhoea causing dehydration and electrolyte disturbances is characteristic of cryptosporidiosis. The presence of fever suggests cytomegalovirus, MAC or *Entamoeba* infestation. Concurrent cytomegalovirus retinitis may occur in association with cytomegalovirus colitis (Figures 6.13).

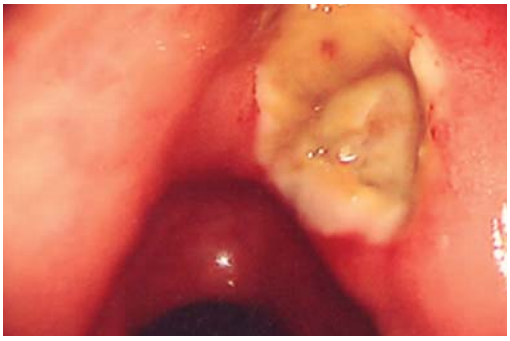

**Figure 6.13**: Deep colonic ulceration caused by cytomegalovirus infection

## Abdominal adenopathy and hepatosplenomegaly

Abdominal adenopathy and hepatosplenomegaly suggest systemic infiltrative processes secondary to MAC, tuberculosis, histoplasmosis or lymphoma. Haematochezia, tenesmus and lower abdominal cramps imply colonic infection (e.g. cytomegalovirus colitis). Large volume watery diarrhoea with mid-abdominal cramps suggests small bowel infection (e.g. *Cryptosporidium*, *Microsporidia*, histoplasmosis or MAC). The diagnosis of HIV enteropathy is used to describe unexplained diarrhoea in patients with HIV infection.

## Abdominal pain

Epigastric pain can be due to cytomegalovirus -related gastritis or ulceration, Kaposi's sarcoma and lymphoma. The ulcerations are often refractory to the usual acid suppression therapy. Multifocal presentation with extensive disease may suggest the presence of gastric lymphoma, which may also cause gastric outlet obstruction. However, visceral lesions and the common finding of "B-symptoms" (a group of symptoms that may be present in people with lymphoma: fever, night sweats and weight loss) may lead clinicians to suspect an opportunistic infection.

Right upper quadrant pain: **acalculous cholecystitis** is a rare but potentially fatal manifestation (Figure 6.14). Several opportunistic infections[10,11] have been implicated (Table 6.2). It can present atypically as unexplained fever, leukocytosis, vague abdominal discomfort and even peritonitis due to gallbladder gangrene and perforation. **AIDS cholangiopathy** develops following post-inflammatory stricture associated with opportunistic infections of the biliary tree.[12]

It is characterised by intermittent right upper quadrant pain and elevated serum alkaline phosphatase level. Jaundice is uncommon as the obstruction is rarely complete. Severe abdominal pain suggests the presence of papillary stenosis. *Cryptosporidium parvum* is the most common pathogen and concomitant diarrhoea may be present.

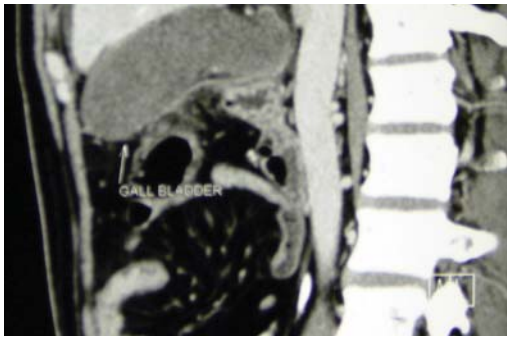


**Figure 6.14**: Acalculous cholecystitis

Diffuse periumbilical pain: **MAC-associated mesenteric lymphadenitis** causes cramping periumbilical pain with weight loss, fever and diarrhoea. **Acute pancreatitis** can rarely be secondary to opportunistic infections and neoplasms (cytomegalovirus, MAC, *Cryptosporidium*, toxoplasmosis, Kaposi's sarcoma and non-Hodgkin's lymphoma).[13,14]

Lower abdominal pain can result from *cytomegalovirus*, *amoebic* infection, lymphoma and appendicitis. Extra-pulmonary tuberculosis is an important differential diagnosis in endemic areas, which often involves the ileocecal region, peritoneum and mesenteric lymph nodes.[15,16]

Intestinal obstruction is often caused by neoplasm, whereas *intussusception* may be due to lymphoma or infections.[17]

Peritonitis and ascites may result from perforated viscus (e.g. cytomegalovirus colitis) and infections (e.g. tuberculosis, MAC, toxoplasmosis, *Cryptococcus* and histoplasmosis).

## Gastrointestinal bleeding

In patients with advanced AIDS, Kaposi's sarcoma and gastroduodenal lymphoma are common causes of upper gastrointestinal bleeding.[18,19]

Lower gastrointestinal bleeding is mostly related to cytomegalovirus colitis, idiopathic colonic ulcers[20] and other causes (e.g. Kaposi's sarcoma, *Bartonella* infection, anorectal disease, herpes simplex virus and non-Hodgkin's lymphoma).

**Anorectal diseases** are frequent among men who have sex with men with receptive anal intercourse.[21] Patients will not divulge the symptoms unless they are directly questioned. Perirectal abscesses, anal fistulae and infectious proctitis are the most common clinical findings.

Tenesmus, perirectal tenderness and rectal discharge are often caused by proctitis secondary to sexually transmissible infections (e.g. herpes simplex virus, gonorrhoea, chlamydia and syphilis).

Other aetiologies of anorectal disease include lymphoma, tuberculous ulcerations, histoplasmosis, anal warts, anal fissure and carcinoma.[22]

Physical examination should include careful inspection of the peri-anal region and the anal canal (for fissures and masses), and palpation of inguinal lymph nodes (for lymphogranuloma venereum).

**Table 6.2: Gastrointestinal manifestations**

| Clinical presentations | Aetiology (frequency) | Associated features | CD4 count (cells/µL) at risk |
|---|---|---|---|
| **Odynophagia and dysphagia** | Candidiasis (50-70%) | - Commonest OI<br>- Dysphagia, diffuse pain | < 100 |
| | CMV (20%) | - Focal odynophagia<br>- Fever common<br>- CMV viraemia (by PCR, antigen, culture) does not establish diagnosis | < 100 |
| | HSV (2-5%) | - Oral ulcers may be present<br>- Focal pain<br>- Fever uncommon | < 100 |
| | Idiopathic ulcers (10-20%) | Focal pain without fever | Any |

Continued over page

**Table 6.2: Gastrointestinal manifestations (Continued)**

| Clinical presentations | | Aetiology (frequency) | Associated features | CD4 count (cells/μL) at risk |
|---|---|---|---|---|
| **Odynophagia and dysphagia** | | Uncommon causes: MTB, MAC, *Histoplasma*, KS, NHL | | Depends on aetiology |
| **Diarrhoea** | **Acute** | *Salmonella* (5-15%) | - Cause septicaemia in 50% HIV cases<br>- Fever, abrupt onset of diarrhoea, abdominal pain<br>- Asymptomatic carrier and relapse common in untreated HIV patients | Any |
| | | *Escherichia coli* (10-15%) | - Self-limiting watery diarrhoea (EPEC)<br>- Traveller's diarrhoea (ETEC)<br>- Bloody diarrhoea without fever (EHEC: O157:H7), causes TTP and HUS in children<br>- Dysentery (EIEC) | |
| | | Enteric virus: norovirus, rotavirus, enteric virus (15-30%) | - Self-limiting watery diarrhoea | |
| | | *Clostridium difficile* (10-15%) | - Recent antibiotic use<br>- Leukocytosis and hypoalbuminemia<br>- Cause pseudomembranous colitis and toxic megacolon | |
| | | *Campylobacter jejuni* (4-8%) | - Watery diarrhoea or dysentery<br>- Improperly cooked food<br>- Resistance to macrolide/ quinolone increasing worldwide, more common in South-East Asia | |
| | | *Shigella* (1-3%) | - Dysentery, tenesmus<br>- Extraintestinal features: headache, seizures, delirium, Reiter's syndrome, HUS<br>- Relapse uncommon | |

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**Table 6.2: Gastrointestinal manifestations (Continued)**

| Clinical presentations | | Aetiology (frequency) | Associated features | CD4 count (cells/μL) at risk |
|---|---|---|---|---|
| | **Chronic** | CMV (15-40%) | - Fever common<br>- Profuse watery/ bloody diarrhoea<br>- Associated with bowel perforation and disseminated CMV infection | < 50 |
| | | *Cryptosporidium parvum* (10-30%) | - Fever (30%)<br>- Profuse watery diarrhoea if CD4 <100 cells/μL<br>- Asymptomatic carrier (4%)<br>- AIDS cholangiopathy | < 200 |
| | | Microsporidiosis (15-20%) | - Fever uncommon<br>- Watery diarrhoea<br>- Multi-organ involvement (CNS, pulmonary, ocular, muscular, renal) and disseminated disease common | < 100 |
| | | MAC (10- 20%) | - Watery diarrhoea, abdominal pain<br>- Fever, wasting common<br>- Bacteraemia and systemic infection | < 50 |
| | | *Cyclospora cayetanensis* (14% in tropical areas, < 1% in nontropical areas) | - Traveller, outbreaks of foodborne illness<br>- More common in tropical climates<br>- Flu-like symptoms, bloating, flatulence, 10% has abdominal pain<br>- Associated with cholecystitis | < 200 |
| | | *Giardia lamblia* (1-3%) | - Asymptomatic to severe diarrhoea and malabsorption<br>- Flatulence, nausea, foul-smelling stool, abdominal cramps<br>- Fever uncommon<br>- Travellers | Any |

Continued over page

**Table 6.2: Gastrointestinal manifestations (Continued)**

| Clinical presentations | | Aetiology (frequency) | Associated features | CD4 count (cells/μL) at risk |
|---|---|---|---|---|
| | | *Entamoeba histolytica* (1-3%) | - Subacute onset, fever common<br>- Chronic diarrhoea/ dysentery<br>- Travellers to endemic areas | Any |
| | | *Isospora belli* (1-2%) | - Endemic in Indochina, South America and South Pacific<br>- Uncommon in non-tropical areas<br>- Peripheral eosinophilia prominent | < 100 |
| | | An extension from acute diarrhoea | *Clostridium difficile, Campylobacter jejuni* | < 200 |
| | | HIV enteropathy (20-30%) | Watery diarrhoea | < 100 |
| **Abdominal pain** | **Acalculous cholecystitis** | CMV, *Cryptosporidia, Microsporidia Campylobacter Isospora* | - Cause gallbladder perforation<br>- 15% no organism identified | < 200 |
| | **AIDS cholangio-pathy** | *Cryptosporidia, Microsporidia,* CMV | - Fever and jaundice uncommon<br>- Combined papillary stenosis and intrahepatic ductal strictures is unique in AIDS cholangiopathy | < 50 |
| | **Gastric diseases** | CMV | Patchy gastritis/ multiple small ulcers | < 100 |
| | | Neoplasm (KS/ NHL) | - Diarrhoea or gastrointestinal bleeding<br>- NHL tends to present as late stage<br>- 40% KS had gastrointestinal involvement | < 100 |
| | **Acute pancreatitis** | Rarely due to OI (CMV, MAC), KS, NHL | Asymptomatic elevation of amylase are common in patients with HIV | Depends on aetiology |

Continued over page

**Table 6.2: Gastrointestinal manifestations (Continued)**

| Clinical presentations | | Aetiology (frequency) | Associated features | CD4 count (cells/µL) at risk |
|---|---|---|---|---|
| **Abdominal pain** | **Mesenteric lymphadenitis** | MAC | Fever, weight loss, diarrhoea | < 50 |
| | **Lower abdominal pain** | MTB, CMV, NHL, amoeba, appendicitis | | Depends on aetiology |
| | **Intestinal obstruction, intussception** | Neoplasm, NHL | | |
| | **Peritonitis and ascites** | Perforated CMV colitis, MTB, MAC, IRIS, toxoplasmosis, *Cryptococcus*, histoplasmosis | | |
| **Gastrointestinal bleeding** | | CMV colitis, KS, idiopathic colonic ulcers, others | | Depends on aetiology |
| **Anorectal diseases** | | Infectious proctitis (gonorrhoea, HSV, *Chlamydia*, syphilis) | - Commonly seen in MSM<br>- Tenesmus, perirectal tenderness and rectal discharge<br>- HSV is the most common cause of perianal ulcerative lesions<br>- HSV may cause urinary symptoms, impotence and sacral paresthesia | Depends on aetiology |
| | | Perirectal abscesses, anal fistulae, ulcerations<br><br>Warts, carcinoma, lymphoma, histoplasmosis | | |

OI: Opportunistic infection; EPEC: Enteropathic *E. coli;*
ETEC: Enterotoxigenic *E. coli;* EHEC: Enterohaemorrhagic *E. coli;*
EIEC: Enteroinvasive *E. coli;* TTP: Thrombotic thrombocytopenic purpura;
HUS: Haemolytic uremic syndrome; MSM: men who have sex with men;

Continued over page

**Table 6.2: Gastrointestinal manifestations (Continued)**

USG: Ultrasonography; GIT: Gastrointestinal tract;
LFT: Liver function test; VDRL: Venereal disease research laboratory;
FTA-ABS: Fluorescent treponemal antibody absorption; MTB: Mycobacterium tuberculosis;
IRIS: Immune Reconstitution Inflammatory Syndrome; KS: Kaposi's sarcoma;
CMV: Cytomegalovirus; MAC: *Mycobacterium avium* complex;
NHL: Non-Hodgkin's lymphoma; CNS: Central nervous system

# References


1. Sirois DA. Oral manifestations of HIV disease. Mt Sinai J Med 1998;65(5-6):322-32.

2. Glick M, Muzyka BC, Salkin LM, Lurie D. Necrotizing ulcerative periodontitis: a marker for immune deterioration and a predictor for the diagnosis of AIDS. J Periodontol. 1994 May;65(5):393-7.

3. King MD, Reznik DA, O'Daniels CM, Larsen NM, Osterholt D, Blumberg HM. Human papillomavirus-associated oral warts among human immunodeficiency virus-seropositive patients in the era of highly active antiretroviral therapy: an emerging infection. Clin Infect Dis 2002;34(5):641-8.

4. Whitby D, Howard MR, Tenant-Flowers M, Brink NS, Copas A, Boshoff C, et al. Detection of Kaposi's sarcoma-associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. Lancet 1995;346:799-802.

5. Biggar RJ, Rosenberg PS, Cote T. Kaposi's sarcoma and non-Hodgkin's lymphoma following the diagnosis of AIDS. Multistate AIDS/Cancer Match Study Group. Int J Cancer 1996;68:754-8.

6. Bini EJ, Micale PL, Weinshel EH. Natural history of HIV-associated esophageal disease in the era of protease inhibitor therapy. Dig Dis Sci 2000;45:1301-7.

7. Wilcox CM, Alexander LN, Clark WS, Thompson SE 3rd. Fluconazole compared with endoscopy for human immunodeficiency virus-infected patients with oesophageal symptoms. Gastroenterology 1996;110:1803-9.

8. Laing RBS, Brettle RP, Leen CLS. Clinical predictors of azole resistance, outcome and survival from oesophageal candidiasis in AIDS patients. Int J STD AIDS 1998;9:15-20.

9. Genereau T, Lortholary O, Bouchaud O, Lacassin F, Vinceneux P, De Truchis P,et al. Herpes simplex esophagitis in patients with AIDS: report of 34 cases. The Cooperative Study Group on Herpetic Esophagitis in HIV Infection. Clin Infect Dis 1996;22:926–31.

10. French AL, Beauder LM, Benator DA. Cholecystectomy in patients with AIDS: clinical pathological correlation in 107 cases. Clin Infect Dis 1995;21:852-8.

11. Blumberg RS, Kelsey P, Perrone T, Dickersin R, Laquaglia M, Ferruci J. Cytomegalovirus and Cryptosporidium associated acalculous gangrenous cholecystitis. Am J Med 1984; 76:1118-23.

12. Cello J. Acquired immune deficiency syndrome-related sclerosing cholangitis: spectrum of disease. Am J Med 1989;86;539-46.

13. Bonacini M. Pancreatic involvement in human immunodeficiency virus infection. J Clin Gastroenterol 1991;13:58.

14. Wilcox CM, Forsmark CE, Grendell JH, Darragh TM, Cello JP. Cytomegalovirus-associated acute pancreatic disease in patients with acquired immunodeficiency syndrome. Report of two patients. Gastroenterology 1990;99:263.

15. Smit SJ, Du Toit RS. The acute AIDS abdomen-a prospective clinical and pathological study. S Afr J Surg 2005;43:88.

16. Sharma MP, Bhatia V. Abdominal tuberculosis. Indian J Med Res 2004;120:305.

17. Wood BJ, Kumar PN, Cooper C, Silverman PM, Zeman RK. AIDS-associated intussusception in young adults. J Clin Gastroenterol 1995; 21:158.

18. Cello JP, Wilcox CM. Evaluation and treatment of gastrointestinal tract haemorrhage in patients with AIDS. Gastroenterol Clin North Am 1988;17:639-48.

19. Parente F, Cernuschi M, Valsecchi L, Rizzardini G, Musicco M, Lazzarin A,et al. Acute upper gastrointestinal bleeding in patients with AIDS: a relatively uncommon condition associated with reduced survival. Gut 1991;32:987-90.

20. Chalasani N, Wilcox CM. Etiology and outcome of lower gastrointestinal bleeding in patients with AIDS. Am J Gastroenterology 1998;93:175-8.

21. Wexner SD, Smithy WB, Milsom JW, Dailey TH. The surgical management of anorectal diseases in AIDS and pre-AIDS patients. Dis Colon Rectum 1986;29:719-723.

22. Li FP, Osborn D, Cronin CM. Anorectal squamous carcinoma in two homosexual men. Lancet 1982;2:391.

# 7 HIV-related eye conditions

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An ocular complication at some point of their illness is a well known entity in AIDS patients. This chapter discusses a broad range of ocular complications that can occur with HIV infection.

## HIV-related eye conditions

A broad range of ocular complications involving the adnexa, eyeball and nerves can commonly occur with human immunodeficiency virus (HIV) infection.

The pattern of ocular involvement in HIV infection has changed over the years with the advent of combination antiretroviral therapy.[1] In general, CD4 cell count has been used to predict the onset of certain ocular infections in patients who have HIV infection (Table 7.1).

**Table 7.1: Ocular complications of HIV infection versus degree of immunodeficiency indicated by CD4 cell count**

| | Type of ocular complication | | |
|---|---|---|---|
| **CD4 cell count** | **Vascular** | **Infection** | **Tumour** |
| ≤ 500 cells/μL | | Herpes zoster ophthalmicus | Kaposi's sarcoma<br>Lymphoma |
| ≤ 200 cells/μL | | Ocular tuberculosis<br>Pneumocystosis | |
| ≤ 100 cells/μL | HIV retinopathy | Toxoplasmic retinitis<br>Progressive outer retinal necrosis<br>Cryptococcal choroidopathy | |
| ≤ 50 cells/μL | | Cytomegalovirus retinitis | |

## Adnexal manifestations

The ocular adnexa consists of the eyelid, the conjunctiva and the lacrimal drainage system.

Common ocular adnexa conditions in patients with HIV infection include blepharitis, dry eyes [referred to below as sicca syndromes], herpes zoster ophthalmicus, Kaposi's sarcoma and molluscum contagiosum.

## Blepharitis and sicca syndromes

Typical symptoms are dryness, burning and a sandy-gritty eye irritation that gets worse as the day goes on. There may also be crusting, discharge or stye formation (Figure 7.1).

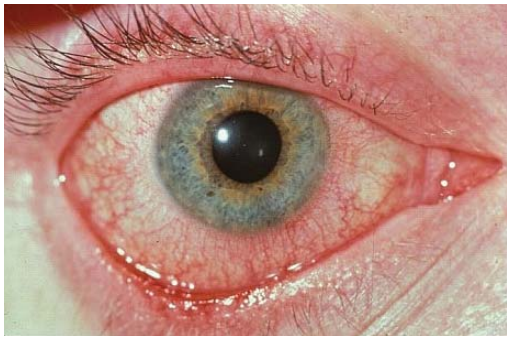

**Figure 7.1:** Seborrhoeic blepharitis
Source: McCluskey PJ. HIV-related eye disease. In:G. Stewart (2nd edition) Could it be HIV? Sydney: Australasian Medical Publishing Company Limited, 1994:30.

## Herpes zoster ophthalmicus

Herpes zoster ophthalmicus occurs in approximately 3-4% of patients with HIV infection.[2,3] It is a painful vesicular dermatitis, which results mostly from the re-activation of latent varicella zoster virus from a previous primary infection. The most common nerve involved is the first division of the trigeminal nerve. The condition results in a painful rash over the forehead, extending down to the eyelid on the same side and may involve the conjunctiva (Figure 7.2).

Ocular complications include stromal and neurotrophic keratitis, anterior uveitis, scleritis and infectious retinitis and cranial nerve palsies and post-herpetic neuralgia.[4]

Herpes zoster ophthalmicus can occur in both people with HIV infection and the general population. In HIV-infected patients, herpes zoster ophthalmicus is extensive and relapsing and occurs in relatively early stage of the disease, when CD4 cell counts are above 200 cells/µl.[3,5]

Although herpes zoster ophthalmicus is not considered an AIDS-defining opportunistic infection, its higher occurrence in patients with HIV infection is generally an indication for HIV testing.[5]

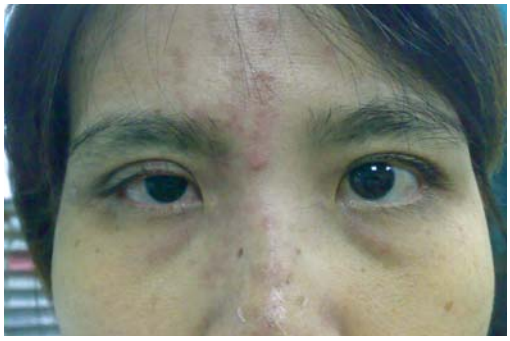

**Figure 7.2:** Herpes zoster vesicular dermatitis involving the first branch of the trigeminal nerve

## Kaposi's sarcoma

Kaposi's sarcoma (KS) is a vascular tumour caused by human herpes virus 8 (HHV-8) and was one of the earliest identified complications of advanced HIV infection.[6] Ocular adnexal KS typically presents as a discrete violet sub-conjunctival lesion or as an eyelid nodule. Patients may present with symptoms of ocular irritation, trichiasis or interference of vision by the lesion.[6,7]

## Molluscum contagiosum

Classically, this viral infection presents as a small number of pearly white lesions with central umbilication and may be associated with conjunctivitis and keratitis.[8] In individuals with HIV infection, the lesions are larger than normal, more disseminated and difficult to eradicate by conventional techniques using curettage, excision or cryotherapy.[9]

Molluscum contagiosum can occasionally be difficult to distinguish from cryptococcal skin infections.[10] A biopsy of these lesions may be indicated to establish the diagnosis.

# Anterior segment manifestations

## Infectious keratitis

Varicella zoster and herpes simplex virus are the most common causes of infectious keratitis in patients with HIV infection. Keratitis due to varicella zoster is usually associated with herpes zoster ophthalmicus and complications include subepithelial infiltrates, stromal keratitis, disciform keratitis, uveitis and secondary glaucoma. Complications of herpes simplex virus infection include dendritic and geographic epithelial keratitis, stromal keratitis and iridocyclitis. Other causes of infectious keratitis are fungal infections, most commonly by candidal species (especially in intravenous drug users) and *Fusarium* or *Aspergillus* species.[11]

# Posterior segment manifestations

## HIV retinopathy

The most common ocular complication of HIV infection is a retinal microvasculopathy called HIV retinopathy. It occurs in 50-70% of patients with CD4 cell counts below 100 cells/μL.[2 5,11] It is mainly characterised by the presence of multiple cotton-wool spots and dot-blot intra-retinal haemorrhages on ocular fundus examination.

The aetiology of this retinopathy has been postulated to be due to HIV infection of the endothelium of the retinal microvasculature (possibly cytomegalovirus induced), and deposition of circulating immune complexes.[12]

Typically, the retinopathy does not affect vision to a degree that is noticed by the patient. Presence of cotton-wool spots and the intra-retinal haemorrhages can also be confused with diabetic retinopathy or other ischaemic diseases in the eye.

# Cytomegalovirus retinitis

Cytomegalovirus retinitis is the most common opportunistic ocular infection and the most important cause of visual loss in patients with AIDS (20% per year for those with CD4 counts ≤ 50 cells/μL), and is an indicator of advanced HIV.[13-15] In some patients, cytomegalovirus retinitis may be the first clinical manifestation of AIDS.

Patients with cytomegalovirus retinitis may be asymptomatic or present with floaters, blurred vision or visual field loss. Lesions usually appear in the retinal periphery as white fluffy areas of necrotising retinitis associated with haemorrhages and vascular sheathing and, if untreated, will eventually spread centrally towards the macula and optic disc, and haematogenously to the other eye.[16] Blindness may result if the macula area is affected or retinal detachment occurs due to breaks in the necrotic retina.

Cytomegalovirus retinitis must be differentiated from other causes of infectious retinitis. Classically, the anterior segment and the vitreous show little inflammation during cytomegalovirus retinitis. Since the lesion may be asymptomatic, patients with very low CD4 cell counts (≤ 100 cells/μl) are advised to have regular ophthalmological checks for early detection of this disease.

**Case study 7.1**

A 20-year-old female university student, who was otherwise healthy, presented to the eye clinic with a one-week history of generalised maculopapular rash, sore throat and decreased vision in the right eye. Vision in the right eye was 20/100 and in the left eye was 20/20. The anterior chamber and the vitreous of the right eye had no gross signs of inflammation. Fundus examination showed a significant area with necrotic retinitis and haemorrhages surrounding the infero-temporalvascular arcade extending up to the optic disc (Figure 7.3). The left fundus was normal.

Continued over page

**Case study 7.1** (Continued)

**Figure 7.3:** Right eye infero-temporal confluent cytomegalovirus retinitis involving the optic disc.

The patient had no history of injecting drug use and had not had a blood transfusion, but did have unprotected sex with a few partners.

A vitreous sample was taken for polymerase chain reaction testing, which gave a positive result for cytomegalovirus. HIV ELISA testing was positive; her CD4 count was 12 cells/μL. Treatment with ganciclovir (intravitreal as well as intravenous) was given for a period of three weeks. She had a total of four doses of intravitreal ganciclovir 2 mg/ 0.1 mL before the retinitis completely resolved and the vision in the right eye improved to 20/30. The generalised rashes disappeared after two weeks of initiating therapy. She was subsequently started on antiretroviral therapy (Figure 7.4).

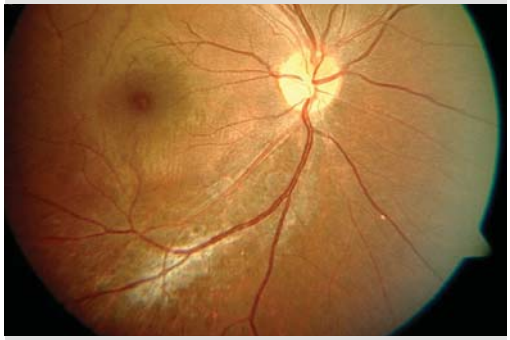

**Figure 7.4:** Six months post-treatment with intravitreal and intravenous ganciclovir, showing resolution of the cytomegalovirus retinitis.

## Toxoplasma retinochoroiditis

Toxoplasmosis is the second most common cause of ocular retinitis in patients with HIV. Unlike immunocompetent patients who usually present with a single, unilateral necrotising lesion next to old scar tissue, patients with HIV may have diffuse or multi-focal lesions (Figure 7.5), involvement of both eyes, and relatively little vitreous inflammation.[17]

In HIV patients, ocular toxoplasmosis may be misdiagnosed as cytomegalovirus retinitis. The following are helpful differentiating signs: in toxoplasmosis, the lesions appear as dense white-yellow exudates with fluffy borders, there is absence of retinal haemorrhage (unlike cytomegalovirus retinitis) and the intraocular inflammation is more marked compared to cytomegalovirus retinitis. Patients with ocular toxoplasmosis frequently have a CD4 cell count higher than that seen with cytomegalovirus retinitis. Toxoplasmosis lesions usually respond well to sulphadiazine (4-6 g/day) or clindamycin (2.4 g/day in four divided doses) and pyrimethamine (100-200 mg loading dose followed by 50-75 mg daily). If sulphadiazine is used, then folinic acid 20-25 mg should be given.

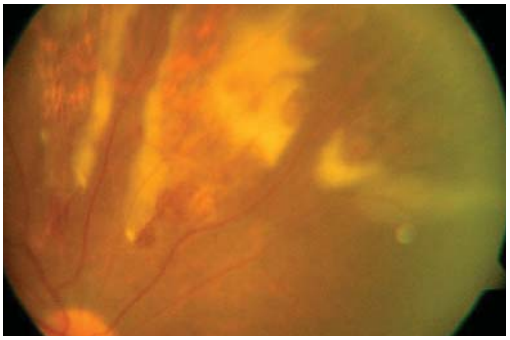

**Figure 7.5:** Toxoplasma retinochoroiditis.

## Ocular syphilis

Ocular syphilis occurs at any degree of immunodeficiency. Ocular syphilis manifests as anterior uveitis, neuroretinitis, chorioretinitis, vitritis, papillitis and retinal vasculitis.[18]

Syphilis should be considered in patients with HIV infection with anterior or posterior uveitis. These patients also seem to have a higher rate of neurosyphilis and should be evaluated by lumbar puncture for cerebrospinal fluid analyses and Venereal Disease Research Laboratory (VDRL) testing.[18,19]

## Tuberculosis

The most common ocular manifestations of tuberculosis are anterior uveitis and disseminated choroiditis, especially in military tuberculosis (Figure 7.6).[20]

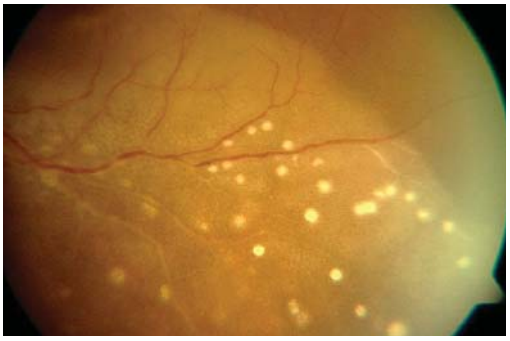

**Figure 7.6:** Disseminated choroiditis in a patient with military tuberculosis.

## Pneumocystis choroidopathy

*Pneumocystis jirovecii* choroidopathy tends to occur in HIV patients with disseminated infection, and has an increased association with the use of aerosolised pentamidine prophylaxis.[21] The disease is characterised by round, yellow-white, subretinal lesions with minimal inflammation. Patients with *P. jirovecii* choroiditis are often asymptomatic.[21,22]

## Cryptococcal chorioretinitis

The most common ocular manifestation of this spore-forming fungus is papilloedema related to cryptococcal meningitis, (Figure 7.7) with subsequent vision loss due to optic atrophy or cortical blindness.[23] Cryptococcal chorioretinitis may occur either via direct extension from the meningeal infection or in association with cryptococcal septicaemia.[24]

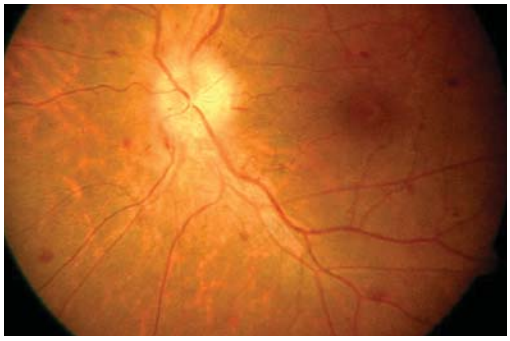

**Figure 7.7:** Optic disc swelling seen in a patient with cryptococcal meningitis

## Conclusion

The ocular presentations of HIV infection will continue to be an important cause of visual morbidity among patients with HIV infection, who are increasingly surviving for longer periods due to improved antiretroviral therapy and better management of opportunistic infections. The recognition of these ocular presentations as potential indicators of advanced HIV infection can provide important opportunities for HIV testing.

## References


1. Jabs DA, Bartlett JG. AIDS in ophthalmology: a period in transition. Am J Ophthalmol 1997; 124:227-33.

2. Jabs DA. Ocular manifestations of HIV infection. Trans Am Ophthalmol Soc 1995; 93:623-83.

3. Margolis TP, Milner MS, Shama A, Hodge W, Seiff S. Herpes zoster ophthalmicus in patients with human immunodeficiency virus infection. Am J Ophthalmol 1998;125:285-91.

4. Choo PW, Galil K, Donahue JG, Walker AM, Spiegelman D, Platt R. Risk factors for postherpetic neuralgia. Arch Intern Med 1997; 157:1217-24.

5. Kempen JH, Jabs DA. Ocular complications of human immunodeficiency virus infection. In: Johnson G, Minassian DC, Weale RA, West SK, editors. The Epidemiology of Eye Disease, 2nd ed. London: Arnold, 2003:318-40.

6. Renwick N, Halaby T, Weverling GJ, Dukers NH, Simpson GR, Coutinho RA, et al. Seroconversion for human herpesvirus 8 during HIV infection is highly predictive of Kaposi's sarcoma. AIDS 1998;12: 2481-8.

7. Shuler JD, Holland GN, Miles SA, Miller BJ, Grossman I. Kaposi's sarcoma of the conjunctiva and eyelids associated with the acquired immunodeficiency syndrome. Arch Ophthalmol 1989;107:858-62.

8. Mansour AM. Adnexal findings in AIDS. Ophthal Plast Reconstr Surg 1993;9:273-9.

9. Merisier H, Cochereau I, Hoang-Xuan T, Toublanc M, Ruggeri C. Multiple molluscum contagio sum lesions of the limbus in a patients with HIV infection. Br J Ophthalmol 1995;79:393-4.

10. Lewis JL, Rabinovich S. The wide spectrum of cryptococcal infections. Am J Med 1972; 53(3):315-22.

11. Cassoux N, Bodaghi B, LeHoang P. Ocular manifestations of AIDS. In: Ben Ezra, editor. Ocular Inflammation-Basic and Clinical Concepts. London: Martin Dunitz Ltd, 1999:427-49.

12. Mueller AJ, Plummer DJ, Dua R, Taskintuna I, Sample PA, Grant I, et al. Analysis of visual dysfunctions in HIV-positive patients without retinitis. Am J Ophthalmol 1997;124:158-67.

13. Kupperman BD, Petty JG, Richman DD, Mathews WC, Fullerton SC, Rickman LS, et al. Correlation between CD4+ counts and prevalence of cytomegalovirus retinitis and human immunodeficiency virus-related noninfectious retinal vasculopathy in patients with acquired immunodeficiency syndrome. Am J Ophthalmol 1993;115:575-82.

14. Jabs DA, Enger C, Bartlett JG. Cytomegalovirus retinitis and acquired immunodeficiency syndrome. Arch Ophthalmol 1989;107:75-80.

15. Holland GN, Pepose JS, Pettit TH, Gottlieb MS, Yee RD, Foos RY. Acquired immune deficiency syndrome. Ocular manifestations. Ophthalmology 1983;90:859-73.

16. Holland GN, Shuler JD. Progression rates of cytomegalovirus retinopathy in ganciclovir-treated and untreated patients. Arch Ophthalmol 1992;110:1435-42.

17. Holland GN, Engstrom RE Jr, Glasgow BJ, Berger BB, Daniels SA, Sidikaro Y, et al. Ocular toxoplasmosis in patients with the acquired immunodeficiency syndrome. Am J Ophthalmol 1988;106:653-67.

18. Margo CE, Hamed LM. Ocular syphilis. Surv Ophthalmol 1992;37:203-20.

19. Feraru ER, Aronow HA, Lipton RB. Neurosyphilis in AIDS patients: initial CSF VDRL may be negative. Neurology 1990;40:541-3.

20. Havlir DV, Barnes PF. Tuberculosis in patients with human immunodeficiency virus infection. N Engl J Med 1999;340:367-73.

21. Dugel PU, Rao NA, Forster DJ, Chong LP, Frangieh GT, Sattler F. Pneumocystis carinii choroiditis after long-term aerosolized pentamidine therapy. Am J Ophthalmol 1990; 110:113-7.

22. Shami MJ, Freeman W, Friedberg D, Siderides E, Listhaus A, Ai E. A multicenter study of Pneumocystis choroidopathy. Am J Ophthalmol 1991;112:15-22.

23. Kestelyn P, Taelman H, Bogaerts J, Kagame A, Abdel Aziz M, Batungwanayo J, et al. Ophthalmic manifestations of infections with Cryptococcus neoformans in patients with the acquired immunedeficiency syndrome. Am J Ophthalmol 1993;116:721-7.

24. Charles N, Boxred C, Small E. Cryotococcosis of the anterior segment in acquired immunedeficiency syndrome. Ophthalmology 1991;99: 813-6.

# 8 HIV-related haematological conditions

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Haematological problems may be the first presentation of human immunodeficiency virus (HIV) infection. Patients may have no symptoms but be referred because of abnormal blood counts or lymphoid disorders. By recognising the possibility of HIV infection, alert health care workers, have the opportunity to offer early treatment to patients and prevent transmission of the infection.

## Thrombocytopenia

Thrombocytopenia is found in 3-40% of individuals with HIV infection.[1] It can be the first presentation, and may occur at any stage of HIV infection. HIV-related thrombocytopenia can be caused by the following:

### Immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) is very common in HIV infection. This condition, characterised by very low platelet counts with an otherwise normal haematocrit and white blood cell count, is caused by an immune-mediated destruction of platelets. Patients with ITP may bruise easily or have petechiae, and bleeding from the gums or other sites. Serious haemorrhage is uncommon.[2]

### Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is very rare, in comparison to ITP. TTP presents with fever, haemolytic anaemia, thrombocytopenia, renal and neurological problems, caused by thrombi forming in small blood vessels affecting multiple organs.

The diagnosis is confirmed by fragmented red blood cells (schistocytes) found on peripheral blood smear. Pregnancy and disseminated intravascular coagulation should be excluded. TTP is a medical emergency requiring plasmapheresis.

**Case study 8.1**

A 32-year-old married woman presented with fever and a platelet count of 32 X $10^9$/L. She was initially diagnosed with dengue fever, but her fever had lasted 14 days, making dengue unlikely. Further history revealed that she had visited her home in rural Thailand three weeks previously. Blood cultures grew *Salmonella enteritidis*. Disseminated intravascular coagulation screening, dengue serology and blood films for malaria were negative. She was treated with intravenous ceftriaxone, but her low platelet counts persisted. The possibility of immune thrombocytopenic purpura and HIV were considered.

On further questioning, she stated she had injected heroin during her first marriage to a drug user seven years before. HIV infection was confirmed and her CD4 cell count was 100 cells/μL. Her thrombocytopenia resolved with antiretroviral therapy. Her second husband tested negative to HIV, and was counselled about transmission precautions.

**Comment**
Thrombocytopenia can have many causes, including sepsis, malaria and dengue fever. However, if immune thrombocytopenic purpura is considered, the patient should have HIV testing and be assessed for risk factors including drug use and previous sexual partners.

## Anaemia

Anaemia is present in 10-20% of patients with HIV infection at diagnosis, and prevalence can range from 66-85% during the course of disease.[2,3] Fatigue, dizziness and shortness of breath may be the main complaint.

There are many possible causes of anaemia in HIV patients, including anaemia of chronic disease and vitamin B12 or other nutritional deficiencies.[3] If there is fever with anaemia, opportunistic infections that infiltrate the bone marrow should be considered, including tuberculosis, disseminated *Mycobacterium avium* complex (MAC), histoplasmosis, leishmaniasis and cytomegalovirus. Human parvovirus B19 infection can also cause severe anaemia that is refractory to blood transfusions but responds to intravenous immunoglobulin (IVIG). Occasionally, investigations for anaemia may reveal an elevated globulin fraction. However, in HIV patients, this finding is due to a polyclonal gammopathy rather than myeloma.[1]

Investigations for anaemia should include a full blood examination, iron studies, vitamin B12 and folate levels. Further testing can be done to exclude haemolysis and gastrointestinal blood loss. Because anaemia is typically a late sign of HIV infection, unexplained anaemia should prompt HIV testing to avoid further delays in diagnosis.

## Neutropenia

Neutropenia (neutrophil count below 1.5 x $10^9$/L) may occur in 10-30% of HIV patients, typically with advanced disease. Patients may have fever, mouth ulcers or infections from Gram-negative bacteremia such as salmonellosis.

Neutropenia can result from the direct effect of HIV in the bone marrow, or from other opportunistic infections including cytomegalovirus, disseminated MAC, tuberculosis, histoplasmosis and leishmaniasis.[1,2]

HIV patients with cytopenias require bone marrow examination to determine the cause and to direct therapy.

**Case study 8.2**

A 35-year-old man presented with fever and pancytopenia. He had oral thrush and tested positive for HIV infection. His CD4 cell count was 28 cells/µL. Computed tomography (CT) scans of the abdomen confirmed an enlarged liver and spleen. His blood counts dropped further: white blood cell count 1.5 x $10^9$/L; haematocrit 20%; platelets 17 x $10^9$/L.

No active cytomegalovirus disease was detected. Bone marrow examination did not reveal lymphoma. He was initially treated with broad-spectrum antibiotics, then clarithromycin and ethambutol for presumptive disseminated MAC. He finally responded to empiric amphotericin B treatment. Fungal culture from a bone marrow aspirate grew *Histoplasma capsulatum* weeks later. The patient eventually went home on oral itraconazole.

**Comment**
Although HIV may be obvious, clarifying the cause of haematological abnormalities can be challenging, given the wide range of pathogens in patients with severe immunosuppression.

## Thrombosis

Rarely, HIV may present with coagulation abnormalities and venous thromboembolism. In patients with advanced HIV and opportunistic infections, immobility from illness may be a risk factor. Another possible cause is lupus anticoagulant and anticardiolipin antibodies which have been detected in HIV patients. These abnormalities are not strongly associated with thrombosis although thromboembolic events including strokes have been reported rarely.[4]

Additional factors include decreased antithrombin levels, deficiencies in protein C and free protein S in some HIV patients. Thromboembolic events such as deep venous thrombosis may also represent the first indication of an HIV-associated malignancy.

# Lymphadenopathy

Enlarged lymph nodes can accompany seroconversion and occur mid-course or late in HIV infection. Painless adenopathy should raise concern for lymphoproliferative disease. Constitutional symptoms such as night sweats, weight loss and fevers can occur with infections as well as lymphoma. Splenomegaly may co-exist with lymphadenopathy. The following are common causes of lymphadenopathy in HIV patients (Table 8.1):

## Acute seroconversion

During HIV seroconversion, patients may present with fever, sore throat, muscle aches and enlarged cervical lymph nodes. A sensitive history may indicate the need for HIV testing.

## Persistent generalised lymphadenopathy

This condition can occur early or late in the infection, and consists of generalised lymph node enlargement typically in the cervical, axillary and inguinal regions that persists for more than three months.

## Infectious lymphadenopathy

Tuberculosis is one of the most common causes of cervical lymphadenitis in resource-limited settings. Diagnosis requires a sputum stain for mycobacteria (acid fast bacilli (AFB) stain) and the culture of an aspirate or biopsy from the lymph node. Pulmonary tuberculosis should be excluded, and a diagnosis of tuberculosis should always prompt screening for HIV. Depending on the patient's age, the location of the lymph nodes, and epidemiological risk factors, several other infections can also cause lymphadenitis, such as non-tuberculous mycobacteria, Epstein-Barr virus, streptococcal infection, toxoplasmosis, bartonellosis and lymphogranuloma venereum.

## Malignancies

Lymphoma occurs late in HIV infection and should be considered in individuals with symptomless lymphadenopathy. HIV screening should be offered.

**Table 8.1: Common causes of lymphadenopathy in HIV patients**

| Clinical entity | Stage of infection | Causes | Diagnostic test |
|---|---|---|---|
| Acute seroconversion | Seroconversion | HIV | HIV serology |
| Persistent generalised lymphadenopathy | Early or late | HIV | Histopathology from biopsy |
| Infectious lymphadenopathy | Early or late | Tuberculosis, MAC, EBV, lymphogranuloma venereum, toxoplasmosis, streptococcus, bartonellosis, other Cytomegalovirus retinitis | Fine needle aspirate or excisional biopsy with microbiological tests, Serology |
| Malignancy | Late | Lymphomas, Kaposi's sarcoma | Histopathology from biopsy |

MAC: *Mycobacterium avium* complex
EBV: Epstein-Barr virus

Given the wide range of possible causes for lymphadenopathy in a person with HIV infection, the clinical approach should include a thorough history, serological testing for appropriate pathogens and close clinical monitoring.

Diagnostic biopsy should be recommended if the clinical presentation suggests an infectious cause (such as fever, which can be a prominent feature of mycobacterial infections), if a dominant lymph node develops (which may suggest lymphoma), or if the lymphadenopathy persists for more than 3 months.

**Case study 8.3**

A 41-year-old man presented with abdominal discomfort for 2 months. He had previously been diagnosed with HIV infection but had not started antiretroviral therapy because his CD4 cell count was over 300 cells/μL and he could not afford to pay for his treatment. He had some weight loss and night sweats. Examination was notable for an abdominal mass. Computed tomography (CT) scans of the abdomen revealed a large mass and associated para-aortic lymphadenopathy. Further investigations demonstrated Stage 4B non-Hodgkin's lymphoma. He received chemotherapy complicated by several episodes of neutropenic fever but remains in remission 2 years later.

**Comment**
Although the risk of malignancies is increased in advanced HIV infection, lymphomas can occur even at higher CD4 cell counts. Further investigations are warranted for constitutional symptoms and weight loss to exclude malignancies such as lymphoma which are an increased risk in persons with HIV infection.

# Malignancies

An estimated 40% of all patients with HIV infection will develop malignancy during the course of their disease.[5] Patients presenting with any of the following malignancies should have HIV testing:

## Lymphoma

HIV-associated lymphomas include primary central nervous system lymphoma and systemic non-Hodgkin's lymphoma. Both are acquired immunodeficiency syndrome (AIDS)-defining illnesses. Primary central nervous system lymphoma is strongly associated with Epstein-Barr virus and causes neurological symptoms, whereas systemic non-Hodgkin's lymphoma can present as a gastrointestinal or renal mass. These lymphomas are usually high-grade and aggressive; prognosis is poor.

Although not considered AIDS-defining, Hodgkin's disease and primary effusion lymphoma also occur with increased incidence among those with HIV infection.

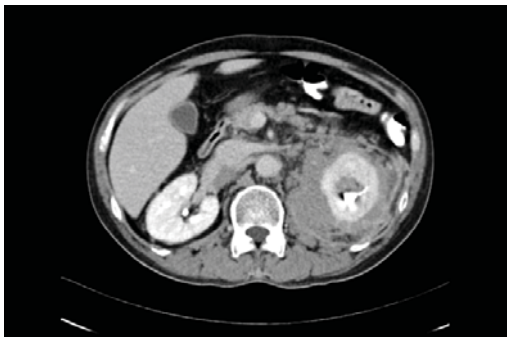

**Figure 8.1:** 49-year-old man with abdominal pain and advanced HIV. Biopsy of the mass encasing his left kidney revealed lymphoma.

## Kaposi's sarcoma

Kaposi's sarcoma is the most common malignancy among persons with HIV infection, with the highest prevalence in men who have sex with men. In fair-skinned individuals, the cutaneous lesions of Kaposi's sarcoma appear as non-tender, violaceous papules or larger plaques, but may appear brown or black on darker complexions. Visceral Kaposi's sarcoma can present with bleeding (gastrointestinal Kaposi's sarcoma) or cough (pulmonary Kaposi's sarcoma).

# References


1. Coyle TE. Hematologic complications of human immunodeficiency virus infection and the acquired immunodeficiency syndrome. Med Clin North Am 1997;81:449-70.

2. Volberding PA, Baker KR, Levine AM. Human immunodeficiency virus hematology. Hematology Am Soc Hematol Educ Program 2003:294-313.

3. Bain BJ. Pathogenesis and pathophysiology of anaemia in HIV infection. Curr Opin Hematol 1999;6:89-93.

4. Liebman HA, Stasi R. Secondary immune thrombocytopenic purpura. Curr Opin Hematol 2007;14:557-73.

5. Mitsuyasu R. Oncological complications of human immunodeficiency virus disease and hematologic consequences of their treatment. Clin Infect Dis 1999;29:35-43.

# 9 HIV-related skin conditions

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Dermatological conditions are common in all stages of human immunodeficiency virus (HIV) infection. As the skin is regularly observed by patients and easily examined by health care workers, dermatological conditions represent a good opportunity for early diagnosis of HIV.

## Introduction

In the Asian and Pacific regions, the initial patient presentation with HIV is often late and often manifests by mucocutaneous complications consistent with falling cell counts and immunity. The range of common skin presentations of HIV is listed in Table 9.1. Studies have demonstrated the inverse relationship between skin disease and cell counts in HIV.[1] Skin manifestations of HIV can present as infectious, non-infectious and neoplastic disease.

**Table 9.1: Common dermatological presentations of HIV**

**HIV likely**

**Inflammatory**
Seroconversion-like eruption

**Infective**
Cutaneous *Cryptococcus*
Cutaneous cytomegalovirus
Oral candidiasis
Cutaneous tuberculosis or other mycobacterial lesions e.g. *Mycobacterium avium intracellularae* complex
Disseminated fungal infections
Bacillary angiomatosis (*Bartonella henselae* infection)

**Other**
Kaposi's sarcoma (associated HHV8 infection)
Eosinophilic folliculitis
Oral hairy leukoplakia (associated with Epstein-Barr virus infection)
Anal carcinoma
Lipoatrophy

**Be suspicious of HIV**

**Inflammatory**
Severe pruritus (pruritic papular eruption may be due to a florid reaction to insect bites)
Severe drug eruption

**Infective**
Human papillomavirus (warts, *Condyloma acuminata*)
Extensive molluscum contagiosum
Herpes zoster
Herpes simplex virus
Crusted scabies (Norwegian scabies)
Primary syphilis (co-infection with HIV)
*Penicillium marneffei* cutaneous lesions

Recognising the HIV-related skin conditions may enable initial HIV diagnosis and also provide clinical confidence in the predicted degree of immunosuppression where CD4 counts are not readily available. Whereas some cutaneous conditions such as oral candidiasis, extensive molluscum contagiosum, eosinophilic pustular folliculitis, cryptococcosis or Kaposi's sarcoma are highly suggestive of HIV disease by their mere presence, other conditions common in the general population are distinguished in HIV infection by their atypical presentation, severity, frequency of recurrence or recalcitrant nature.[2]

## Clinical presentations

Presentation of skin disease in HIV may either be typical or atypical:

i) Typical presentation of a common skin disease e.g. seborrhoeic dermatitis

ii) Atypical presentation of common disease e.g. extensive warts

iii) Typical presentation of an uncommon disease e.g. Kaposi's sarcoma

iv) Atypical presentation of uncommon disease e.g. cutaneous tuberculosis

v) Unique condition in HIV e.g. oral hairy leukoplakia, lipoatrophy.

## Seroconversion illness

The seroconversion eruption classically presents as a transient, generalised measles-like eruption on the trunk and extremities of the body but may be associated with vesicles and oral ulcers (Figure 9.1). Systemic features include fever, lethargy, myalgias and lymphadenopathy. This condition may go unnoticed by the patient.

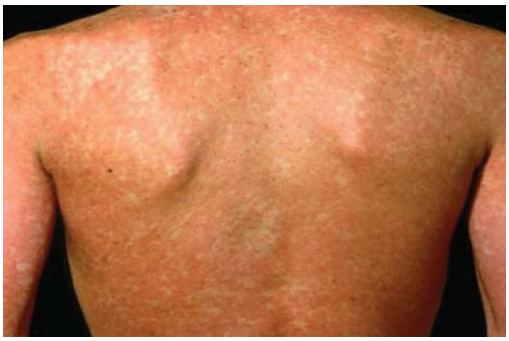
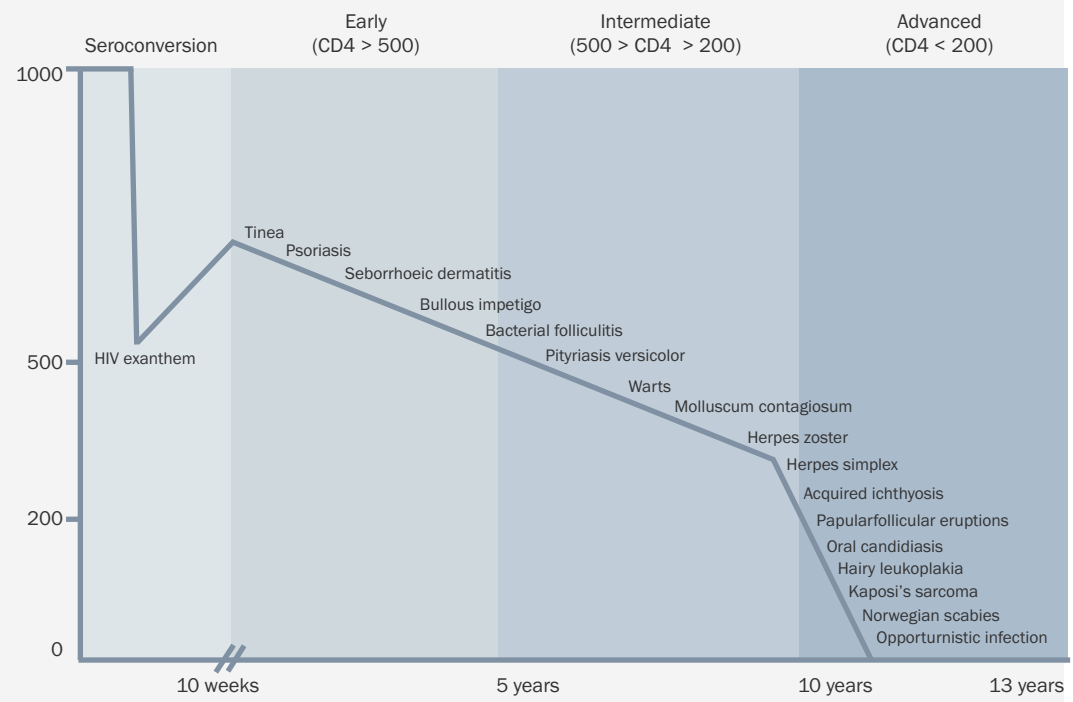


**Figure 9.1:** Seroconversion eruptions. Used with permission from Professor J Gold, Albion Street Clinic, Sydney.

## Timeline of cutaneous change with the loss of CD4 cells

HIV-related skin change represents a continuum along which patients may present (Figure 9.2). After seroconversion, skin diseases may follow along general population demographics with no signs of infection during early asymptomatic HIV disease.

In the next stage of HIV, skin presentations represent disease progression with opportunistic infections or acquired immunodeficiency syndrome (AIDS)-defining illnesses due to falling immunity. Since the advent of antiretroviral therapy, HIV skin disease is also seen in the clinical context of immune reconstitution inflammatory syndrome, with a spectrum of systemic or local inflammatory, infective, autoimmune or malignant disease with rising cell counts.[3,4]




| | Seroconversion | Early (CD4 > 500) | Intermediate (500 > CD4 > 200) | Advanced (CD4 < 200) |
|---|---|---|---|---|
| Diagnosis | Childhood-type maculopapular exanthem in at-risk individual, predominent truncal involvement, infectious mononucleosis-like symptoms | As for immunocompetent patients | Consider skin biopsy and possible culture | Skin biopsy and culture are vital for accurate diagnosis |
| Management | HIV test at time of presentation and repeat 3 months later | As for immunocompetent patients | Treatment resistance may occur<br><br>Be prepared to review diagnosis<br><br>Prescribe prophylactic treatment to prevent recurrence | Unusual presentations are usual<br><br>First time therapies often fail<br><br>Review regularly<br><br>Prescribe prophylactic treatment for candidiasis, herpes simplex, seborrhoeic dermatitis, icthyosis/ xeroderma, warts/mollusca and folliculitis |

Modified from: Wong D, Shumack S. HIV and skin disease. In: Stewart G, editor. Managing HIV. Sydney: Australasian Medical Publishing Company Ltd. 1997;63.

**Figure 9.2**: Timeline of cutaneous change with the loss of CD4 cells

# Viral infections

## Herpes (varicella) zoster

HIV should be considered in patients less than 40 years old presenting with herpes zoster. The typical presentation is a grouped vesicular (blistering) eruption involving one or more dermatomes with prodromal pain.[5,6] The lesions become pustular and haemorrhagic within a few days, then crusting and scaring occurs (Figure 9.3). In HIV, the ulceration is often more extensive, deeper, prolonged, and the scarring more severe. Atypical, disseminated and chronic herpes zoster infections are usually in the setting of advanced HIV disease or immune reconstitution inflammatory syndrome.[7] In children with HIV who develop chickenpox, there is a higher risk of subsequently developing herpes zoster and they are more likely to have recurrent episodes. [8]

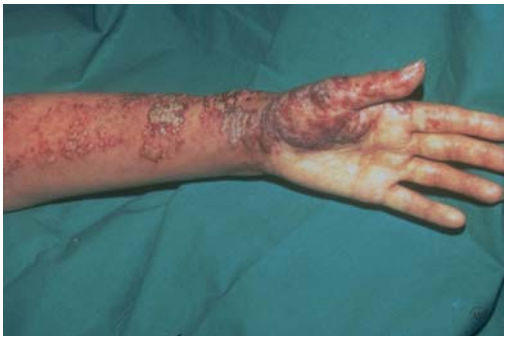


**Figure 9.3:** Hand involvement of herpes zoster. Used with permission from the American Academy of Dermatology.

## Herpes simplex viruses

These viruses include herpes simplex virus 1 and 2 (HSV-1 and HSV-2). They are common causes of acute and chronic skin lesions of grouped vesicles on an erythematous base (Figure 9.4). Chronic herpes simplex virus is more common in HIV and may present as indolent perioral and anogenital ulcerations, which may be painful (Table 9.2).

Recently studies have shown the association between HSV-2 infection and the risk of acquiring HIV. HIV-1 is shed from genital ulcers caused by HSV-2.[9]

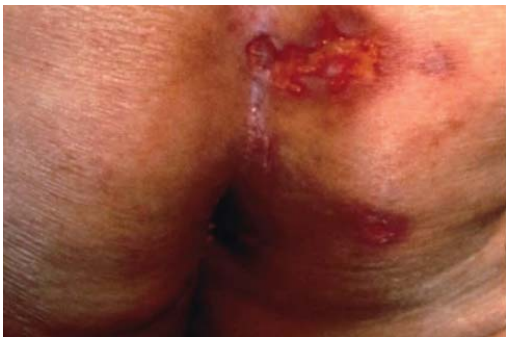


**Figure 9.4:** Perianal herpes simplex. Used with permission from the American Academy of Dermatology.

## Human papillomavirus

Human papillomavirus commonly causes warts in the context of both the general population and those with HIV infection. Warts in the context of HIV may be more pronounced, recalcitrant to therapy and in more unusual locations such as:

The forearm (Figure 9.5):

**Table 9.2: Presentations of herpes simplex**

| Condition | Affected area of the body |
|---|---|
| Herpes labialis | Lips and perioral area |
| Herpes genitalis | Genital area |
| Herpes gladiatorum | Buttocks |
| Herpetic whitlow | Fingers and around the nails |
| Herpetic keratoconjunctivitis | Eyes |
| Eczema herpeticum | Areas of eczema (may be widespread) |
| Neonatal herpes | In newborns |
| Herpes encephalitis | Central nervous system |

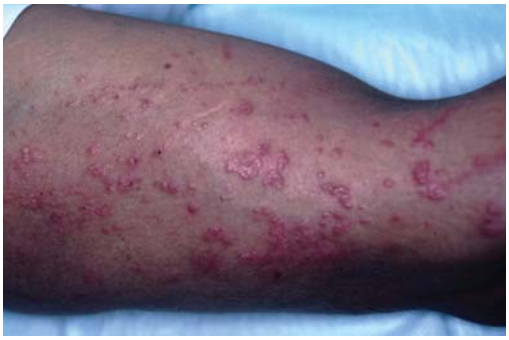


**Figure 9.5:** Inflamed, extensive flat warts of the forearm, more obvious as they resolve after ART commenced. Used with permission from Dr M Whitfeld of St Vincent's Hospital, Sydney.

Lips (Figure 9.6):

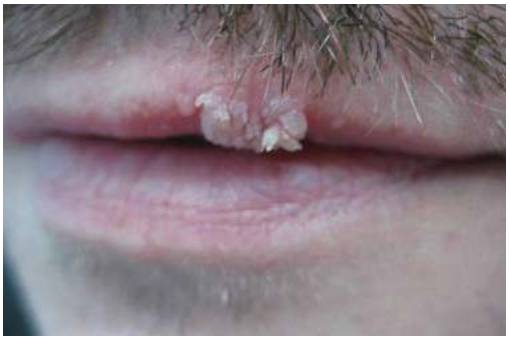


**Figure 9.6:** Unusual location lip wart in HIV. Used with permission from Dr M Whitfeld of St Vincent's Hospital, Sydney.

# Fungal infection

**Fungal infections** may present as persistent and recurrent skin disorders. Common superficial fungal infections include candidiasis and generalised dermatophytosis caused by *Trichophyton rubrum*. Deep fungal infections of note include cryptococcosis, histoplasmosis or penicillinosis which may signify systemic disease.

***Penicillium marneffei*** is endemic in tropical Asia and can cause a fatal systemic mycosis in patients with HIV. It is the third most common opportunistic infection in patients with AIDS in Asia after tuberculosis and *Cryptococcus*. Disseminated *P. marneffei* infection in HIV can present as cutaneous lesions, appearing in 75% of patients who have penicilliosis.

Typical skin lesions are umbilicated papules with a central necrotic core on the face and neck, less commonly on the limbs and torso. The differential diagnosis includes molluscum contagiosum, histoplasma and *Cryptococcus*.[10]

**Cutaneous cryptococcosis** may manifest with cellulitis, papules, plaques, ulcers or translucent papules with central umbilication, resembling molluscum contagiosum. Cutaneous histoplasmosis is due to haematogenous spread and is endemic in South-East Asia. It can also present with papules, ulcers, acneiform or cellulitis-like eruptions.[7, 11]

**Seborrhoeic dermatitis** is a common condition, affecting as much as 85% of patients with HIV.[12] It can present at any CD4 cell count, but with deteriorating counts it is often extensive, more severe and has a reduced response to treatment. Pityrosporum yeast (Malassezia) has a role in this disease. Patients with HIV characteristically have more erythema and extensive involvement in the sebaceous areas of the scalp and nasolabial folds than those without HIV (Figure 9.7). Sites such as the chest, back, axillae and intertriginous zones are more commonly involved.[13]

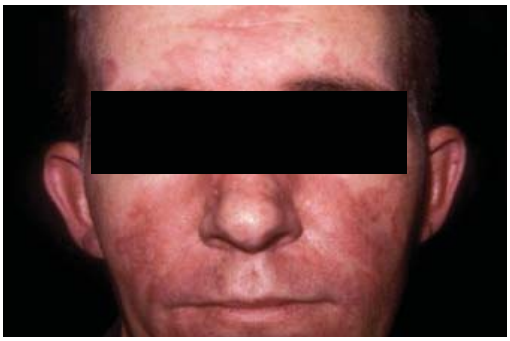


**Figure 9.7:** Photo of marked facial seborrhoeic dermatitis in the setting of HIV. Used with permission from Dr Toby Maurer, University of California San Francisco.

# Other Infections

## Syphilis

With the resurgence of clinical presentations of syphilis, syphilitic chancres should alert the clinician to the possibility of HIV; they are believed to increase HIV transmission.

Chancres are often more severe in the setting of HIV.[14,15] The primary chancre presents as a painless ulcer 14-21 days after exposure (but often up to 90 days), and may be on the genitalia, perianal area, anal canal or oral cavity. Secondary syphilis has a wide variety of presentations, however, it is most commonly widespread and maculopapular or papulos-quamous in morphology.[16]

The differential diagnosis of secondary syphilis is often broad and multiple causes are possible in the general population and in the setting of HIV, including pityriasis rosea, drug eruptions, psoriasis, lichen planus and acute febrile exanthems.[17] Concurrent primary and secondary syphilis are more common in HIV.

### Scabies

In the setting of patients with HIV infection, the classic form as well as crusted scabies can occur. The classic form can occur at any CD4 cell count, while crusted scabies occurs at CD4 counts below 150 cells/μL. Classic scabies presents as papulovesicular lesions (Figure 9.8). The distribution varies, favouring the wrists, interdigital web spaces, elbows, axillae, breasts and genitals. Due to the associated pruritus and excoriation, bacterial superinfection may occur with impetigo, cellulitis and in some cases fatal sepsis.[18] With HIV, the number of mites can increase unchecked, thus producing a more severe form of scabies or crusted scabies, in which there is marked thickening, often plaques, papules and crusting of the skin, particularly on the hands. The entire body including the head may be involved.[19,25]

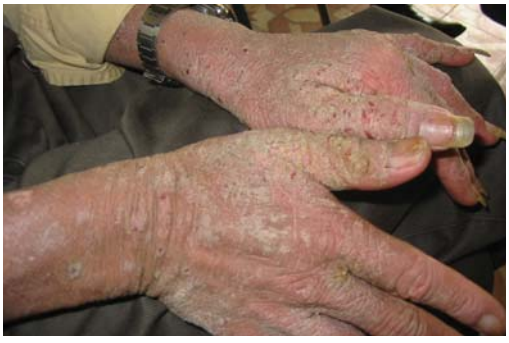


**Figure 9.8:** Exaggerated scabies of the hand. Used with permission from HIV Treatment and Care, Family Health International, Vietnam.

For **Molluscum contagiosum** see Chapter 7, HIV-related eye conditions.

## Malignancy

**Kaposi's sarcoma** presents often with pigmentation evolving from erythematous macules of the skin that can develop into plaques and nodules, may ulcerate or disseminate and commonly involves the mucosa (Figure 9.9). It presents most frequently with CD4 counts below 200 cells/μL but can occur at any stage.[20,15]

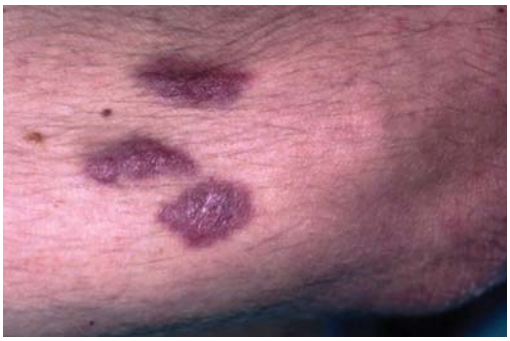


**Figure 9.9:** Kaposi's sarcoma of the forearm. Used with permission from Dr M Whitfeld of St Vincent's Hospital, Sydney.

**Anal carcinoma**, **penile intraepithelial neoplasia** and **cervical intraepithelial neoplasia** are papillomavirus-associated malignancies that can be more common, progressive and aggressive in those with HIV. Perianal, anal and penile intraepithelial neoplasia classically present as velvety erythematous or hyperpigmented defined plaques.[16,17]

## Other presentations

For **oral candidiasis** and **oral hairy leukoplakia** see Chapter 6, HIV-related oral and gastrointestinal conditions.

### Eosinophilic folliculitis

Eosinophilic folliculitis presents as intensely pruritic 2-3 mm pruritic, erythematous, oedematous, urticarial papules centred around follicles and may have central vesicles or pustules.

The distribution is over the forehead, neck, shoulders, trunk and upper arms.

Secondary changes resulting from scratching are common, and include excoriations with secondary staphylococcal infection, prurigo nodularis, lichen simplex chronicus and post–inflammatory pigmentary changes. Clinically, it is most commonly seen in those not on antiretroviral therapy with advanced HIV with CD4 cell counts below 300 cells/μL.[3, 18]

## Pruritus

Itch is one of the most common symptoms in patients with HIV and has multiple causes including skin infections, infestations, insect bites, papulosquamous disorders, xerosis and drug reactions (Figure 9.10).

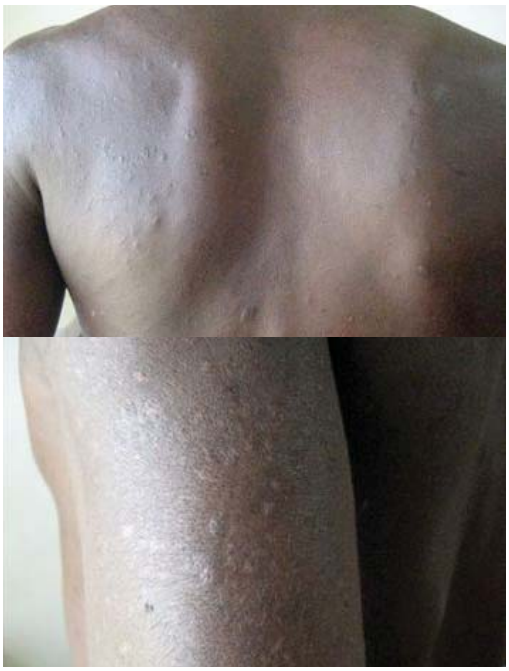


**Figure 9.10:** Left arm demonstrating the presentation of papular pruritic eruption (PPE) of HIV. Used with permission from Dr Toby Maurer of University of California, San Francisco.

# Adverse drug reactions on and off antiretroviral therapy

Drug eruptions are common and can present in a variety of contexts both on and off antiretroviral therapy. Drug eruptions are the most common cause of erythroderma in patients with HIV. Commonly measles-like drug eruptions can occur in as many as 65% of patients on sulfamethoxazole for *Pneumocystis* pneumonia treatment and prophylaxis.

Erythematous macules and papules can become generalised, persisting even after therapy cessation. Sulfonamides also cause urticaria, erythema multiforme, Steven Johnson's syndrome, and potentially life-threatening skin shedding called toxic epidermal necrolysis. Other frequently used medications that can cause toxic epidermal necrolysis in undiagnosed HIV include penicillin antibiotics or fluconazole. Antiretroviral drugs such as nevirapine can cause mild to severe skin rashes, including toxic epidermal necrolysis, but rashes associated with other antiretroviral drugs are usually not severe.[19,20]

**Case study 9.1**

Mr AS is a 39-year-old man. He is a homosexual and has a history of injecting drug use. Recently he has been given a course of penicillin antibiotic therapy for a newly diagnosed penile syphilitic chancre. He has developed diffuse, total body erythema with an additional rash on his hands and back following his first dose of antibiotics (Figures 9.11 and 9.12).

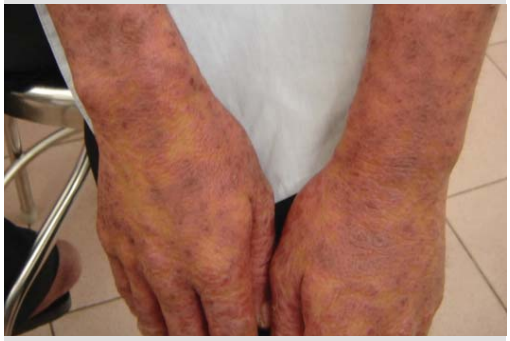


**Figure 9.11:** Skin rash on the hands. Used with permission from HIV Treatment and Care, Family Health International, Vietnam.

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**Case study 9.1** (Continued)

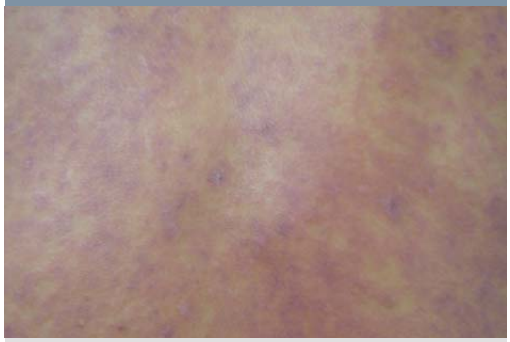

**Figure 9.12:** Skin rash on the back. Used with permission from HIV Treatment and Care, Family Health International, Vietnam.

## Questions to consider

- Could it be HIV – when and how would you do an HIV test?
- What is your differential diagnosis of this skin rash?
- What other clinical conditions do you need to think about?
- What investigations are necessary?

He tested positive for HIV (rapid and confirmatory ELISA tests) and a rapid plasma reagin (RPR) test & and a Venereal Disease Research Laboratory test were positive for *Treponema pallidum*. This skin eruption was thought to be due to a drug reaction to the penicillin or syphilis.

## Therapy options

- Benzathine penicillin G 1.8 g (2.4 million units) intramuscularly as one dose followed by procaine penicillin 3 g (3 million units) intramuscularly daily plus probenecid 500 mg orally every 6 hour a day for 10 days.

- For patients who are allergic to penicillin: doxycycline 200 mg orally daily for 20 days or tetracycline HCl 500 mg orally 6 hourly for 20 days.

# Conclusion

Given the visual nature of skin disease, being familiar with cutaneous signs of HIV and being able to determine immune status by the examination of the skin are of great value, particularly in resource-limited settings. It is important to suspect HIV in patients presenting with recalcitrant, recurrent or multiple skin conditions. These may complicate internal whole body disease i.e. systemic illness. Early recognition of HIV presenting as skin disease is essential for initiation of management of both the dermatological disease and HIV.

# References


1. Nnoruka E, Chukiwuka J, Anisuiba B. Correlation of mucocutaneous manifestations of HIV/AIDS infection with CD4 counts and disease progression. The International Society of Dermatology. 2007;46(2):14-18.

2. Waugh, M. Skin diseases- clinical indicator of immune status in HIV infection. Int J Dermatol 2007;44(8):705-6.

3. Lehloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. Dermatol Clin 2006;24(4):549-70.

4. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS 2004;18(12):1615-27.

5. Wareham DW, Breuer J. Herpes zoster. Br Med J 2007;334:1211.

6. Dworkin R, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. Clin Infect Dis 2007:44:S1-S26.

7. Hogan, MT. Cutaneous infections associated with HIV/AIDS. Dermatol Clin 2006;24:473-95.

8. Gershon AA, Mervish N, La Russa P, Steinberg S, Lo SH, Hodes D, et al. Varicella-zoster virus infection in children with underlying human immunodeficiency virus infection. J Infect Dis 1997;176:1496-500.

9. Nagot N, Ouedraogo A, Foulongne V, Konaté I, Weiss HA, Vergne L, et al. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. N Engl J Med 2007;356:790-9.

10. Vanittanakom N, Cooper C, Fisher M, Sirisanthana T. Penicillium marneffei infection and recent advances in the epidemiology and molecular biology aspects. Clin Microbiol Rev 2006;19(1):95-110.

11. Venkatesan P, Perfect J, Myers S. Evaluation and management of fungal infections in immunocompromised patients. Dermatol Ther 2005;18:44-57.

12. Kreuter A, Schugt I, Hartmann M, Rasokat H, Altmeyer P, Brockmeyer NH. Dermatological diseases and signs of HIV infection. Eur J Med Res 2002;7:57-62.

13. Diova N, Mosam A. Inflammatory non-infectious dermatoses of HIV. Dermatol Clin 2006;24(4);439-48.

14. Rompalo AM, Lawlor J, Seaman P, Quinn TC, Zenilman JM, Hook EW III. Modification of syphilitic genital ulcer manifestations by co-existent HIV infection. Sex Transm Dis. 2001;28:448-54.

15. Schofer H, Imhof M, Thoma-Greber E, Brockmeyer NH, Hartmann M, Gerken G, Pees HW, Rasokat H, Hartmann H, Sadri I, Emminger C, Stellbrink HJ, Baumgarten R, Plettenberg A. Active syphilis in HIV infection: a multicentre retrospective survey. The German AIDS Study Group (GASG). Genitourin Med 1996; 72:176-81.

16. Stevenson J, Heath M. Syphilis and HIV infection; an update. Dermatol Clin 2006;24:497-507.

17. Dylewski J, Duong M. The rash of secondary syphilis. Can Med Assoc J 2007;176(1):33-5.

18. Hengge U, Currie BJ, Jäger G, Lupi O, Schwartz RA. Scabies: a ubiquitous neglected skin disease. Lancet Infect Dis 2006;6(12);769-79.

19. Johnston G. Scabies: diagnosis and treatment. Br Med J 2005:331(7517);619-22.

20. Ponthoff A, Brockmeyer N. HIV-associated Kaposi sarcoma: pathogenesis and therapy. J Dtsch Dermatol Ges 2007;5(12):1091-4.

21. Wilkins K, Turner R, Dolev J, LeBoit PE, Berger TG, Maurer TA. Cutaneous malignancy and human immunodeficiency virus disease. J Am Acad Dermatol 2006;54(2):189-206.

22. Heart A, Whitfeld M, Hillman R. Anal intraepithelial neoplasia and anal cancer in dermatological practice. Australasian J Dermatol 2007;48(3):143-55.

23. Hagensee ME, Cameron JE, Leigh JE, Clark RA. Human papillomavirus infection and disease in HIV-infected individuals. Complications of HIV disease or treatment. Am J Med Scii 2004;328(1):57-63.

24. Diova N, Mosam A. Inflammatory non-infectious dermatoses of HIV. Dermatol Clin 2006;24(4);439-48.

25. Todd G. Adverse cutaneous drug eruptions and HIV: a clinician's global perspective. Dermatol Clin 2006;24(4):459-72.

26. Eisman S. Pruritic papular eruption in HIV. Dermatol Clin 2006;24(4);449-57.

# 10 HIV-related hepatitis

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Health care workers should be aware that hepatobiliary manifestations of human immunodeficiency virus (HIV) are common and patients presenting with conditions due to viral and mycobacterial infections and malignancies should be offered HIV testing.

## Introduction

Hepatobiliary complications are common among individuals with HIV, with abnormal liver function tests seen in 80% at some point during the course of their disease. Co-infections with other viruses (hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A virus (HAV), cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV) and adenoviruses) constitute the major causes of acute and chronic hepatitis.[1-4] Apart from these viral infections, other opportunistic infections and malignancies (e.g. tuberculosis, atypical mycobacteria, cryptosporidiosis and malignancies like Non-Hodgkin's lymphoma and Kaposi's sarcoma), and drug toxicities (from drugs used for opportunistic infection treatment such as antituberculous and antiretroviral drugs like nevirapine and protease inhibitors) are also important causes of hepatitis in these patients.[5-7]

Finally non-HIV-related factors might also contribute to hepatotoxicity (e.g. alcohol use). Biliary disorders include acquired immunodeficiency syndrome (AIDS)-related cholangiopathy (associated with cytomegalovirus, *Mycobacterium avium* complex (MAC), *Cryptosporidia*) are usually seen in advanced HIV disease.

Use of combination antiretroviral therapy (cART) has dramatically reduced the incidence of most opportunistic infections. However liver-related diseases or complications (particularly associated with HBV/HCV co-infection) have increased, causing significant morbidity and mortality.[8-14]

Apart from hepatotoxicity associated with the use of some antiretrovirals, metabolic complications can also involve the liver.

## History

Important points here include: eliciting a history of high-risk sexual exposures (including past and current sexually transmitted infections), injecting drug use, tattooing, body piercing and receipt of blood or blood product transfusions,[15] organ transplant, maintenance haemodialysis, vaccination history, past medical history (opportunistic infections, tuberculosis or CD4 cell counts), medication history (tuberculosis and antiretroviral therapy), use of alternative therapies, alcohol use and family history of liver disease.

## Symptoms and signs

Presentation of acute hepatitis may vary from asymptomatic (common with acute HCV hepatitis) to fulminant hepatic failure. Many patients with marginal elevations of biochemical markers of hepatic injury may be initially asymptomatic. During the prodromal phase (commonly seen with viral hepatitis), patients may present with nausea, anorexia, vomiting, malaise, fatigue, body ache, arthralgias, alterations of taste and fatigue and listlessness.

Soon, patients may complain of a dark yellowish discoloration of urine, sclera and the passage of pale coloured stools. Patients may also complain of abdominal bloating and right upper quadrant pain. Fulminant hepatic failure may be complicated by hepatic encephalopathy.

Progression of acute to chronic hepatitis varies according to the hepatitis virus involved and age at infection.

Chronic hepatitis is common with HBV (around 5% of adults and 90% of infants who acquire the infection at birth) and HCV (around 70-80%, chronicity is higher in patients with HIV co-infection) and absent in HAV and hepatitis E virus (HEV) infections. Patients with chronic hepatitis are mostly asymptomatic with diagnosis made on findings of elevated biochemical markers (transaminases) on routine laboratory testing. Few patients may present with gastrointestinal distress and fatigue. Symptoms of acute hepatitis (see above) may occur during acute flares.

The presence of ascites, and a history of haematemesis (melaena), and encephalopathy are indicative of hepatic cirrhosis. Signs of liver cell failure, cirrhosis and portal hypertension include palmar erythema, gynaecomastia, alopecia, parotid enlargement, spider naevi, hepatomegaly and splenomegaly. Altered sleep rhythm or personality changes and constructional apraxia are the earliest symptoms and signs of hepatic encephalopathy.

Physical examination may reveal icterus and occasionally hepatomegaly. Signs of portal hypertension may be present in cirrhotic patients. Other clues for the aetiology may include lymphadenopathy (tuberculosis, non-Hodgkin's lymphoma), cachexia (non-Hodgkin's lymphoma, tuberculosis), respiratory signs (tuberculosis, *Pneumocystis jirovecii* pneumonia) and retinitis (cytomegalovirus).

Extra-hepatic manifestations are common with chronic HCV infection (and rarely with chronic HBV infection) and include glomerulopathies, mixed cryoglobulinemia, thrombocytopenia, arthritis, thyroid disorders and peripheral neuropathy.

Laboratory evaluation may consist of:

- Full Blood Count (FBC)
- Urea and electrolytes
- Liver function tests
- Alpha fetoprotein
- Coagulation markers
- Alpha 1 antitrypsin
- Iron and copper studies
- Autoantibody studies
- Hepatitis B serology and HBV DNA viral load
- Hepatitis C serology genotype and viral load
- Liver biopsy
- Liver ultrasound
- Non-invasive markers of liver fibrosis include elastometry (fibroscan)[18-20] or serum biochemical indexes (i.e. fibrotest, aspartate aminotransferase to platelet ratio index).[21-24]

The above tests may be available to a greater or lesser extent depending on the country and setting. Table 10.1 depicts the markers used for diagnosis of various stages of HBV infection.

**Table 10.1: Serodiagnosis of viral hepatitis B**

| Test | Acute HBV | Past immunity | Previous vaccine | Immune tolerant | Chronic HBeAg+ | Chronic HBeAg- | Inactive carrier |
|---|---|---|---|---|---|---|---|
| HBsAg | + | - | - | + | + | + | + |
| Anti-HBs | - | + | + | - | - | - | - |
| HBeAg | + | - | - | + | + | - | - |
| Anti_HBeAg | - | +/- | - | - | - | + | + |
| Anti-HBc | IgM+ | Total + | - | + | + | + | + |
| HBV DNA (copies/mL) | + | - | - | >100 000 | >100 000 | >10 000 | - or low + |
| ALT | Elevated | Normal | Normal | Normal | Elevated | Elevated | Normal |

All patients with HIV infection should be screened for HBV and HCV co-infections. HCV and HBV serology tests may be falsely negative in patients with HIV infection and advanced immunosuppression.

An algorithm for the evaluation of patients presenting with acute hepatitis is depicted below (Figure 10.1).

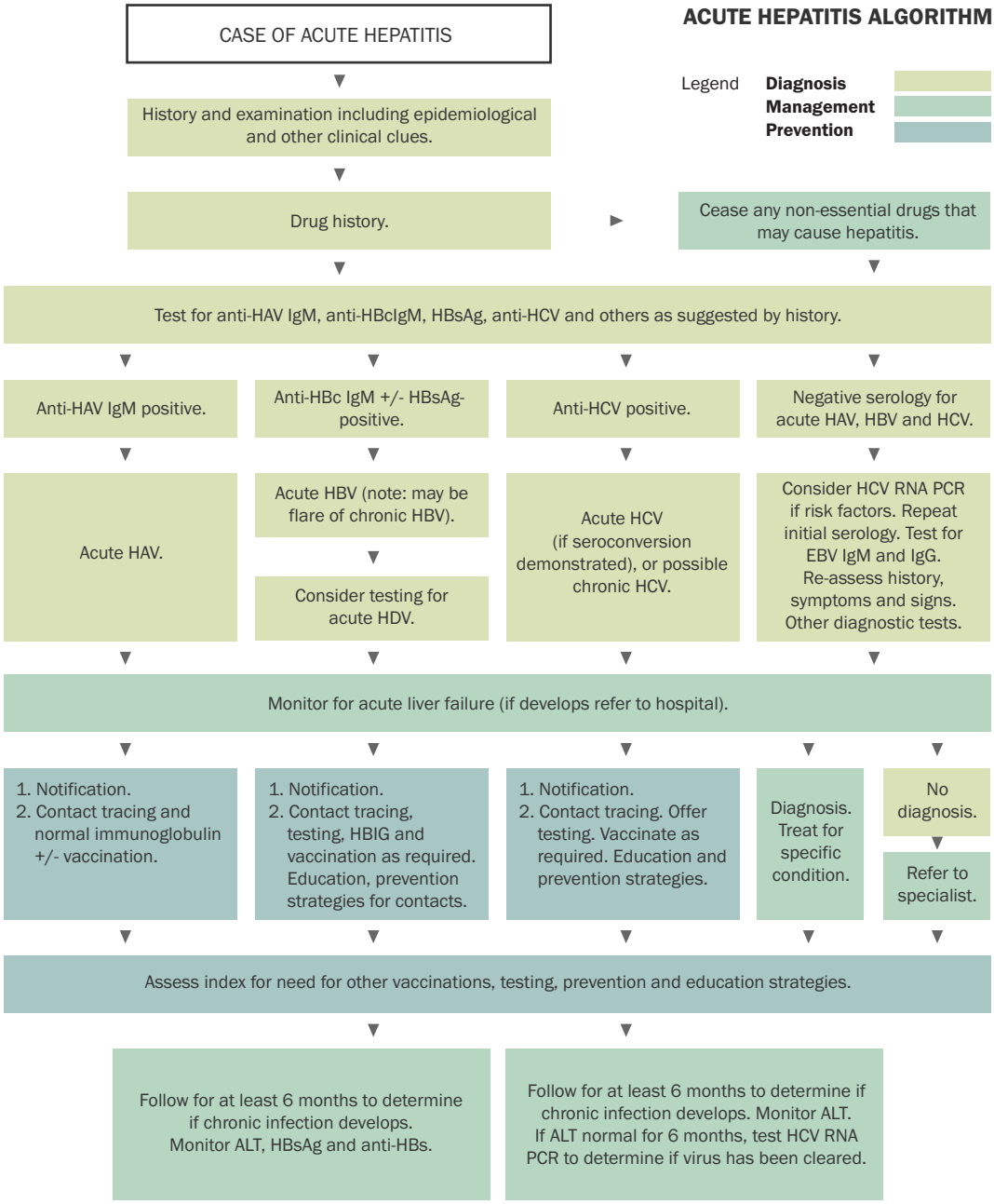


**Figure 10.1:** Algorithm for the evaluation of a patient with acute hepatitis (from HIV, viral hepatitis and STIs: a guide for primary care. Darlinghurst: Australasian Society for HIV Medicine (ASHM), 2008:58)

## Hepatitis and combination antiretroviral therapy

The mechanisms of antiretroviral-induced hepatic toxicity include dose-dependent toxicity, idiosyncratic reactions, hypersensitivity reactions, mitochondrial toxicity and immune reconstitution.[25] Antiretroviral drugs, particularly nevirapine and ritonavir-boosted protease inhibitors, may cause hepatitis (26-31).[26-31] The risk of development of hepatitis is higher in patients with pre-existing liver problems, especially those with HBV and HCV co-infection.[32-34]

The incidence of life threatening hepatitis is higher when nevirapine is initiated at CD4 cell counts above 250 cells/μL in women and CD4 cell counts above 400 cells/μL in men.[26,29] Hepatitis may also occur as part of a hypersensitivity reaction associated with nevirapine use.[35] All ritonavir-boosted protease inhibitors are associated with hepatitis, but it is more common with tipranavir.[36] Ritonavir does not contribute to hepatoxicity when used in low doses. The incidence of severe hepatotoxicity is high in patients taking rifampicin and a ritonavir-boosted protease inhibitor, particularly with lopinavir/ritonavir and saquinavir/ritonavir.[37]

Indirect hyperbilirubinemia (presenting as scleral icterus) is common with the use of atazanavir and indinavir, and generally is not indicative of hepatic damage. Hepatoxicity may be associated with the long-term use of nucleoside analogues (e.g. zidovudine, stavudine, didanosine) mainly driven by mitochondrial toxicity. Nucleoside analogues also may contribute to the occurrence of hepatic steatosis, which is associated with insulin resistance, dyslipidaemia and lipodystrophy.[38-40]

Early onset hepatitis (within 1-4 weeks of initiation of antiretroviral therapy) is usually mediated through an immune mechanism and is more commonly seen with drugs like abacavir and nevirapine. Late onset hepatitis (after 4-8 months of antiretroviral therapy initiation) is because of direct cumulative toxicity of antiretrovirals like stavudine. didanosine, nevirapine, ritonavir, tipranavir and darunavir .[41]

Hepatitis may also occur in HBV/HCV co-infected patients after initiation of cART due to immune reconstitution inflammatory syndrome.[42-44] Withdrawal of antiretroviral drugs with anti-HBV activity (i.e. tenofovir and lamivudine/ emtricitabine) can also lead to hepatitis flares.[45]

## Hepatitis and drugs for treatment of opportunistic infections

Hepatotoxicity is associated with the use of therapies for the treatment of opportunistic infections, especially those used to treat tuberculosis.[46] First-line anti-tuberculosis drugs like pyrazinamide, rifampicin, and isoniazid and most second-line drugs are hepatotoxic. Isoniazid may cause hepatitis in the course of treatment (6 months-1 year), while the others generally cause hepatitis within weeks of initiation.

## Summary

Hepatitis commonly occurs in patients with HIV infection. The major aetiologies include co-infection with hepatotropic viruses (particularly HBV and HCV), opportunistic disease processes, toxicities of antiretroviral drugs and drugs used for the treatment of opportunistic infections, and sometimes factors unrelated to HIV infection like chronic alcohol use. Screening for HBV and HCV is critical in people with HIV infection. Careful use or avoidance of antiretrovirals known to cause hepatotoxicity in high-risk patients is important. Early diagnosis and management of hepatitis can avoid significant morbidity and mortality.

**Case study 10.1**

A 37-year-old man was diagnosed with HIV in July 2004. His baseline CD4 count was 153 cells/μL. The patient was clinically asymptomatic and was started on a regimen of stavudine/lamivudine/nevirapin by his private practitioner.

Continued over page

**Case study 10.1** (Continued)

The patient continued to take the antiretroviral regimen regularly until May 2005, and then stopped it on his own, as he was feeling better with an almost 5 kg weight gain. Follow-up CD4 counts and plasma viral load reports were not done. The patient was 3 years off antiretroviral therapy and presented to another clinic in July 2008 with symptoms of anorexia, nausea, vomiting and fatigue of two weeks duration. On examination he was icteric with a palpable liver two finger breadths below the right costal margin. The rest of the examination was unremarkable.

Investigations revealed that the patient had a CD4 count of 89 cells/μL. Liver function tests showed increased AST and ALT (both three times above normal), direct hyperbilirubinemia and normal alkaline phosphatase. Full blood count revealed a normocytic normochromic anaemia. The patient was HBsAg and HBeAg positive with a plasma HBV viral load above 750 000 copies/mL. An abdominal ultrasound showed no evidence of cirrhosis or portal hypertension. Liver biopsy was not performed.

The patient's IgM-HBc antibody was positive, consistent with an acute HBV infection. In view of the past history of exposure to antiretroviral therapy, the patient was restarted on a regimen of stavudine/lamivudine/efavirenz and adefovir was added to help prevent the development of HBV drug resistance. Within two weeks, the patient felt clinically better and his icterus resolved. After 4 weeks, his liver function tests normalised. At 6 months, his HBV and HIV viral loads were undetectable. He was switched from stavudine/lamivudine/efavirenz to tenofovir/emtricitabine/efavirenz.

## References


1 Hoffmann CJ, Thio CL. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. Lancet Infect Dis 2007;7(6):402-9.

2. Mertens T, Tondorf G, Siebolds M, Kruppenbacher JP, Shrestha SM, Mauff G, et al. Epidemiology of HIV and hepatitis B virus (HBV) in selected African and Asian populations. Infection 1989;17(1):4-7.

3. Zhou J, Dore GJ, Zhang F, Lim PL, Chen YM. Hepatitis B and C virus coinfection in The TREAT Asia HIV Observational Database. J Gastroenterol Hepatol 2007;22(9):1510-8.

4. Gupta S, Singh S. Hepatitis B and C virus co-infections in human immunodeficiency virus positive North Indian patients. World J Gastroenterol 2006;12(42):6879-83.

5. Boyle BA. Recent advances in the management and treatment of GI and hepatic diseases associated with HIV: Part I. AIDS Read 2001;11(7):354-61, 363.

6. Poles MA, Dieterich DT. Infections of the liver in HIV-infected patients. Infect Dis Clin North Am 2000;14(3):741-59.

7. Sidiq H, Ankoma-Sey V. HIV-related liver disease: infections versus drugs. Gastroenterol Clin North Am 2006;35(2):487-505.

8. Anderson KB, Guest JL, Rimland D. Hepatitis C virus coinfection increases mortality in HIV-infected patients in the highly active antiretroviral therapy era: data from the HIV Atlanta VA Cohort Study. Clin Infect Dis 2004;39(10):1507-13.

9. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. Clin Infect Dis 2001;32(3):492-7.

10. Bonacini M, Louie S, Bzowej N, Wohl AR. Survival in patients with HIV infection and viral hepatitis B or C: a cohort study. AIDS 2004;18(15):2039-45.

11. Carter M. ART and liver-related mortality in HIV/HCV. IAPAC Mon 2003;9(12):315.

12. del Amo AJ, Hernandez-Aguado I, Perez-Hoyos S. Effect of HAART on liver-related mortality in patients with HIV/HCV coinfection. Lancet 2004;363(9408):570.

13. Lang L. Viral hepatitis is leading cause of death in people infected with human immunodeficiency virus. Gastroenterology 2007;133(1):7.

14. Lewden C, Salmon D, Morlat P, Bevilacqua S, Jougla E, Bonnet F, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. Int J Epidemiol 2005;34(1):121-30.

15. Chow MP, Lin CK, Lin JS, Chau WK, Ho CH, Chen SY, et al. HIV, HBV and HCV seropositivity in hemophiliacs. Zhonghua Min Guo Wei Sheng Wu Ji Mian Yi Xue Za Zhi 1991;24(4): 339-44.

16. Soriano V, Puoti M, Peters M, Benhamou Y, Sulkowski M, Zoulim F, et al. Care of HIV patients with chronic hepatitis B: updated recommendations from the HIV-Hepatitis B Virus International Panel. AIDS 2008;22(12): 1399-410.

17. Soriano V, Barreiro P, Martin-Carbonero L, Vispo E, Garcia-Samaniego J, Labarga P, et al. Update on the treatment of chronic hepatitis C in HIV-infected patients. AIDS Rev 2007; 9(2):99-113.

18. de L, V, Douvin C, Kettaneh A, Ziol M, Roulot D, Marcellin P, et al. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients. J Acquir Immune Defic Syndr 2006;41(2):175-9.

19. Vergara S, Macias J, Rivero A, Gutierrez-Valencia A, Gonzalez-Serrano M, Merino D, et al. The use of transient elastometry for assessing liver fibrosis in patients with HIV and hepatitis C virus coinfection. Clin Infect Dis 2007;45(8):969-74.

20. Barreiro P, Martin-Carbonero L, Nunez M, Rivas P, Morente A, Simarro N, et al. Predictors of liver fibrosis in HIV-infected patients with chronic hepatitis C virus (HCV) infection: assessment using transient elastometry and the role of HCV genotype 3. Clin Infect Dis 2006;42(7):1032-9.

21. Ngo Y, Munteanu M, Messous D, Charlotte F, Imbert-Bismut F, Thabut D, et al. A prospective analysis of the prognostic value of biomarkers (FibroTest) in patients with chronic hepatitis C. Clin Chem 2006;52(10):1887-96.

22. Bailly F. [Severe hepatopathies in HIV patients. Assessment of fibrosis: hepatic biopsy, Fibrotest]. Med Mal Infect 2004;34 Spec No 2:4-6.

23. Ramos PC, Marcilla F, Lopez G, Hueso E, Pascual A, Aguirre JM. [Valuation of APRI and Forns models for non-invasive diagnosis of fibrosis in patients with hepatitis C in coinfected and non-coinfected with HIV]. An Med Interna 2007;24(8):369-74.

24. Snyder N, Nguyen A, Gajula L, Soloway R, Xiao SY, Lau DT, et al. The APRI may be enhanced by the use of the FIBROSpect II in the estimation of fibrosis in chronic hepatitis C. Clin Chim Acta 2007;381(2):119-23.

25. Nunez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. J Hepatol 2006;44(1 Suppl):S132-S139.

26. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. J Acquir Immune Defic Syndr 2004;35(5):538-9.

27. Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. J Infect Dis 2002;186(1):23-31.

28. Gonzalez de RD, Nunez M, Jimenez-Nacher I, Soriano V. Liver toxicity caused by nevirapine. AIDS 2002;16(2):290-1.

29. Revised nevirapine insert. AIDS Patient Care STDS 2001;15(2):103-4.

30. FDA alerts doctors to Prezista's possible link to liver damage, deaths. AIDS Read 2008;18(5):235.

31. McGovern B. Hepatic safety and HAART. J Int Assoc Physicians AIDS Care (Chic Ill ) 2004;3 Suppl 2:S24-S40.

32. Pineda JA, Santos J, Rivero A, Abdel-Kader L, Palacios R, Camacho A, et al. Liver toxicity of antiretroviral combinations including atazanavir/ritonavir in patients co-infected with HIV and hepatitis viruses: impact of pre-existing liver fibrosis. J Antimicrob Chemother 2008;61(4):925-32.

33. Aceti A, Pasquazzi C, Zechini B, De BC. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV: the role of hepatitis B and C virus infection. J Acquir Immune Defic Syndr 2002;29(1):41-8.

34. Saves M, Raffi F, Clevenbergh P, Marchou B, Waldner-Combernoux A, Morlat P, et al. Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. The APROCO Study Group. Antimicrob Agents Chemother 2000;44(12):3451-5.

35. Knudtson E, Para M, Boswell H, Fan-Havard P. Drug rash with eosinophilia and systemic symptoms syndrome and renal toxicity with a nevirapine-containing regimen in a pregnant patient with human immunodeficiency virus. Obstet Gynecol 2003;101(5 Pt 2):1094-7.

36. Julg B, Bogner JR, Goebel FD. Severe hepatotoxicity associated with the combination of enfuvirtide and tipranavir/ritonavir: case report. AIDS 2006;20(11):1563.

37. Drug-induced hepatitis with saquinavir/ritonavir + rifampin. AIDS Clin Care 2005;17(3):32.

38. Neau D, Winnock M, Castera L, Bail BL, Loko MA, Geraut L, et al. Prevalence of and factors associated with hepatic steatosis in patients coinfected with hepatitis C virus and HIV: Agence Nationale pour la Recherche contre le SIDA et les hepatites virales CO3 Aquitaine Cohort. J Acquir Immune Defic Syndr 2007;45(2):168-73.

39. Zeremski M, Talal AH. Dideoxynucleoside analogues should be used cautiously in patients with hepatic steatosis. Clin Infect Dis 2006;43(3):373-6.

40. Ristig M, Drechsler H, Powderly WG. Hepatic steatosis and HIV infection. AIDS Patient Care STDS 2005;19(6):356-65.

41. Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. AIDS 2007;21(9):1073-89.

42. O'Leary JG, Zachary K, Misdraji J, Chung RT. De novo autoimmune hepatitis during immune reconstitution in an HIV-infected patient receiving highly active antiretroviral therapy. Clin Infect Dis 2008;46(1):e12-e14.

43. Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection, despite lamivudine therapy as part of HAART. Clin Infect Dis 2004;39(1):129-32.

44. Behrens GM, Meyer D, Stoll M, Schmidt RE. Immune reconstitution syndromes in human immuno-deficiency virus infection following effective antiretroviral therapy. Immunobiology 2000;202(2):186-93.

45. McGovern B. What drives hepatitis B virus-related hepatic flares? Virus, T cells--or a bit of both? Clin Infect Dis 2004;39(1):133-5.

46. Pukenyte E, Lescure FX, Rey D, Rabaud C, Hoen B, Chavanet P, et al. Incidence of and risk factors for severe liver toxicity in HIV-infected patients on anti-tuberculosis treatment. Int J Tuberc Lung Dis 2007;11(1):78-84.

# 11 HIV infection in paediatric practice

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Paediatric patients with human immunodeficiency virus (HIV) infection may present in many ways. Appropriate treatment of children with HIV infection requires identification as soon as possible to prevent aggressive disease progression.

## Introduction

HIV infection in Asian children is primarily transmitted through perinatal infection. Most Asian countries except Thailand and India are at an early stage of their local epidemics. Guidelines usually focus on how to diagnose HIV-exposed children, protocols for prophylaxis of opportunistic infections, and management of antiretroviral treatment. It can be difficult for health care workers to decide whether and when they should consider HIV infection in a paediatric patient. However, as children progress more rapidly to acquired immunodeficiency syndrome (AIDS) than adults,[1,2] it is essential to identify and test HIV-exposed infants and children and refer them into HIV care as soon as possible. In addition, children may be the first members of their family to present with acute symptoms of HIV and can lead to opportunities to test and treat their parents. This chapter is intended to deal with clinical situations commonly found in children with HIV infection and how to interpret these situations to rule-in or rule-out HIV.

## When should you suspect HIV infection?

Paediatric patients with HIV infection may present in many ways. Early symptoms may be interpreted as routine childhood illnesses rather than as possible signs of immune compromise. For example, health care workers may not think of HIV in cases of unexplained fever, recurrent middle ear infection, or persistent oral thrush in an older child (Figure 11.1).

A key piece of history is parental HIV status. However, families may be reluctant to disclose this information due to fears of stigma and discrimination. It may be helpful to first obtain clues about potential HIV risks through asking about a history of maternal health problems (e.g. frequent infections, weight loss), illicit drug use by either parent, transfusions to child or parents, and sex-related risks (e.g. multiple or new partners).

HIV infection should be suspected in the following clinical situations:

- Recurrent oral thrush after 6 months of age
- Poor growth (e.g. unexplained reduced weight gain or weight loss)
- Severe or frequent infections (e.g. pneumonia, sepsis, otitis media, zoster – Figure 11.2)
- Developmental delay (e.g. failure to attain, or loss of, common milestones).

**Figure 11.1:** Oral thrush in a 6 year-old boy with HIV.

Late-stage conditions, such as fungal sepsis, viral pneumonia, chronic diarrhoea, and wasting can occur when immune deficiency is severe.

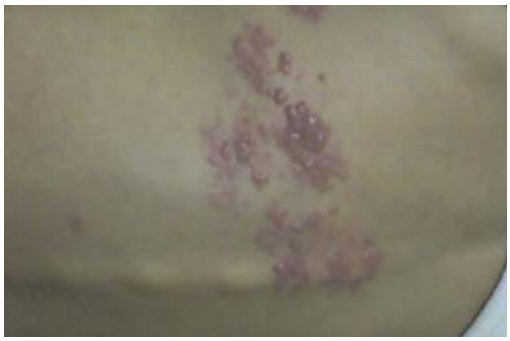

**Figure 11.2:** Varicella-zoster infection

Health care workers should consider obtaining an HIV test whenever there are clinical signs and symptoms (Table 11.1), and suspicion or confirmation of parental HIV.

In children with evidence of severe immunosuppression or life-threatening conditions, the absence of parental risk factors should not discourage HIV testing.

**Table 11.1: Selected clinical criteria and diagnostic clues to HIV in children with correlating WHO HIV staging***

| Clinical category | Clinical finding | WHO stage |
|---|---|---|
| General: | - Failure to thrive: severe wasting or malnutrition | 4 |
| | - Chronic diarrhoea due to parasitic infection | 4 |
| | - Hepatosplenomegaly | 2 |
| Pulmonary: | - Persistent respiratory distress | 4 |
| | - Hypoxia not related to respiratory distress | 3 |
| | - Unexplained digital clubbing | 3 |
| | - Pulmonary tuberculosis | 3 |
| Head and neck: | - Unexplained microcephaly | 4 |
| | - Chronic stomatitis secondary to herpes virus | 4 |
| | - Oral thrush unresponsive to therapy or in children > 6 weeks | 3 |
| | - Persistent or recurrent parotid swelling | 2 |
| | - Severe otitis media or sinusitis | 2 |
| Skin: | - Extensive wart virus infection | 2 |
| | - Extensive molluscum contagiosum | 2 |
| | - Recurrent folliculitis | 2 |
| | - Severe eczematous or seborrhoeic dermatitis | 2 |
| | - Papular pruritic rashes | 2 |
| Neurological: | - Unexplained developmental delay or loss of milestones | 4 |
| | - Unexplained spasticity | 4 |

* Source: WHO. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: Towards universal access. Recommendations for a public-health approach. 2006. Available at: http://www.who.int/hiv/pub/guidelines/art/en/index.html. Cited 26 April 2008

## HIV testing

HIV testing should take age and breastfeeding practices into consideration. Although standard HIV antibody tests (i.e. EIA/ELISA) are reliable in children over 18 months of age, World Health Organization (WHO) guidelines encourage virological testing to determine HIV status in younger infants and children.[2] However, if virological testing is not available, HIV exposure can be determined through antibody testing of the mother or infant. This will provide a basis for presumptive clinical diagnosis before confirmatory testing can be done after 18 months of age.

## Tuberculosis and HIV

In tuberculosis -endemic countries, it is common for individuals with HIV infection to develop tuberculosis at some stage, especially before antiretroviral therapy is started. The diagnosis of tuberculosis in children with HIV is difficult since tuberculosis can mimic a number of other infections. There are several studies describing diagnostic approaches for tuberculosis, mostly using algorithms, diagnostic classifications and point scoring systems. The approach to diagnosing tuberculosis in children with HIV is generally similar as for children without HIV (Table 11.2).

**Table 11.2: WHO-recommended approach to diagnosing tuberculosis[4]**

| |
|---|
| Careful history taking, including history of tuberculosis contacts and symptoms consistent with tuberculosis. |
| Clinical examination including growth assessment. |
| Tuberculin skin testing. |
| Mycobacteriological examinations of sputum, gastric wash specimens, or tissue, whenever possible. |
| Investigations relevant for suspected pulmonary tuberculosis and suspected extrapulmonary tuberculosis. |
| Routine HIV testing in high-prevalence areas. |

The presence of the following should strongly suggest the diagnosis of tuberculosis.[3,4]

- Chronic symptoms and signs suggestive of tuberculosis (subacute onset, fever, weight loss, chronic cough).
- A positive tuberculin skin test (diameter of induration > 5 mm).
- Chest x-ray suggestive of tuberculosis.

**Case study 11.1**

A 2-year-old boy was brought to the outpatient clinic with suspected pneumonia for the third time in 12 months. His mother passed away due to suspected brain tumour at the age of 23 years. The primary caregiver was his grandmother. His father's whereabouts and health status were unknown. A chest x-ray showed a right-sided white out, inconsistent with his symptoms and clinical examination (Figures 11.3 and 11.4).

The child had a normal white blood cell count with relative lymphocytosis, elevated erythrocyte sedimentation rate (ESR), and a negative tuberculin skin testing (TST). The HIV antibody test was positive with very low CD4 percentage (7% or 384 cells/μL). On further questioning, it was found that the mother was taking tuberculosis drugs prior to her death. Pulmonary tuberculosis was suspected in the child, who was immediately started on anti-tuberculosis drugs.

After 2 months of directly observed tuberculosis treatment (DOTS), repeated chest x-ray revealed dramatic improvement, and antiretroviral therapy (zidovudine-lamivudine-nevirapine) was then initiated with the help of the local adherence team and the continued support of the tuberculosis DOTS program.

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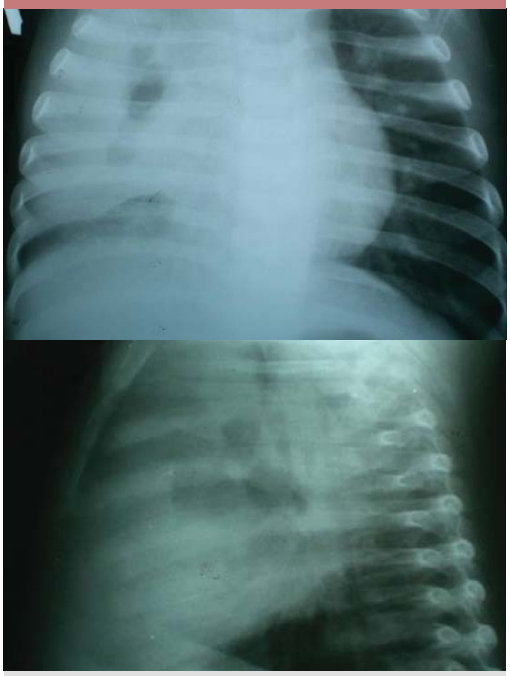
**Case study 11.1** (Continued)



**Figures 11.3** and **11.4:** A chest x-ray showed a right-sided white out

## Chronic diarrhoea

Diarrhoea is a common clinical manifestation in HIV infection that can progress in severity as the immune status deteriorates. There are several potential aetiologies, including infectious pathogens (e.g. bacteria, mycobacteria and viruses), HIV itself and malabsorption.

In cases of acute diarrhoea, HIV may not be included in the initial differential diagnosis. However, the presence of unusual pathogens or progression to chronic diarrhoea is an indicator that the child may have HIV and should be tested.

In known children with HIV infection, chronic diarrhoea is also a clinical marker of disease progression. Specific diagnostic testing should be obtained to evaluate for parasites (e.g. *Giardia, Cryptosporidium*) and less common pathogens (e.g. *Candida*, mycobacteria) to facilitate specific treatment.

Organisms such as non-pathogenic *Escherichia coli* or *Blastocystis hominis* can be causes of diarrhoea in these children and should generally be treated.

## Malnutrition

The following indicators of growth failure, malnutrition and failure to thrive should be included during routine nutritional assessments and can be indicators of progressive HIV disease: [5-7]

- Weight loss of up to -2 standard deviations (SD), not explained by inadequate feeding or concurrent infections, and not responding to nutritional supplementation.
- Single measurement of weight for length (or height) < 70% or -3 SD (protein-energy malnutrition, marasmus) without or with oedema of both feet (protein-energy malnutrition, kwashiorkor or marasmic kwashiorkor).
- Middle upper arm circumference for age < -3 standard deviations (SD) in children aged 6 months – 5 years.

After initial evaluation, whether in inpatient or outpatient settings, it is important to examine specific causes of malnutrition in order to address them, including: [8]

- Poor access to food – inability of the family to provide adequate or appropriate food for a child's level of physical development.
- Inadequate food intake – inability of the child to eat enough to keep up with the higher daily energy requirements of children with HIV due to oral disease (e.g. aphthous or herpetic ulcers), encephalopathy or other conditions.
- Malabsorption – inability of the child to absorb nutrients due to chronic diarrhoea or vitamin/mineral deficiencies. HIV should be considered when there is a discrepancy between access to food and growth and development status.

Nutrition management is crucial and growth recovery may be slow when malnutrition is seen in combination with opportunistic infections. In cases of severe malnutrition and wasting, hospitalisation may be necessary in order to provide an opportunity to address multiple organ systems, and antiretroviral therapy can be considered for initiation during the hospitalisation period.

# References


1. Zeichner SL, Read JS, editors. Handbook of Pediatric HIV Care. 1st edition. Cambridge University Press, 2006.

2. World Health Organization (WHO). Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: Towards universal access. Recommendations for a public-health approach. 2006.

   Available at: http://www.who.int/hiv/pub/-guidelines/art/en/index.html (Cited 26 April 2008)

3. Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. Int J Tuberc Lung Dis 2002;6:1038-45.

4. World Health Organization (WHO). Guidance for National Tuberculosis Programmes on the management of tuberculosis in children. WHO/HTM/TB/2006.371. Geneva, Switzerland: WHO,2006.

5. World Health Organization (WHO). Pocket Book of Hospital Care for Children: guidelines for the management of common illnesses with limited resources. 2005.

   Available at: http://whqlibdoc.who.int/publications/2005/9241546700.pdf (Cited 30 April 2008).

6. Myatt M, Kara T, Collin S. A review of methods to detect cases of severely malnourished children in the community for their admission into community-based therapeutic care program. Food Nutr Bull. 2006;27(3):S7-S23.

7. Mei Z, Grummer-Strawn LM, de Onis M, Yip R. Teh development of MUAC-for-height reference, including a comparison to other nutritional status screening indicators. Bull World Health Org 1997:75:333-41.

8. WHO SEARO. Management of HIV Infection and Antiretroviral Therapy in Infants and Children, A Clinical Manual, 2006.

   Available at: http://www.searo.who.int/en/-Section10/Section18/Section356_12675.htm (Cited 26 April 2008)

# 12 HIV infection in obstetrics and gynaecological settings

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Human immunodeficiency virus (HIV)-exposed infants should be identified as soon as possible, which can be best accomplished through identification of women with HIV infection before and during pregnancy. Conditions such as persistent vulvovaginal candidiasis, recurrent bacterial vaginosis, cervical intraepithelial neoplasia, cervical cancer and sexually transmitted infections (STIs) should encourage provider-initiated counselling and testing.

## HIV in pregnant women

In 2007, UNAIDS estimated that there were 15.4 million adult women and 2.5 million children living with HIV.[1] The majority of infections in children occurs from mother-to-child transmission.[1] The risk of mother-to-child transmission could be reduced from 13-43%[2] to less than 1% with comprehensive management including HIV counselling and testing, antiretroviral prophylaxis or treatment for the mother and infant, modified obstetric practices, and avoidance of breastfeeding.[3]

The overall coverage of prevention of mother-to-child transmission programs and uptake of services that are provided through these programs are still very low worldwide, especially in resource-limited settings.[4]

The lack of knowledge of HIV serostatus is a key factor limiting the potential for widespread use of prevention of mother-to-child transmission programs.[4] Improving the availability, acceptability and quality of HIV testing and counselling services may encourage more women to learn their HIV status and to access HIV treatment and prevention of mother-to-child transmission interventions.

Voluntary counselling and testing or provider-initiated counselling and testing should be routinely available at the first visit or as early as possible to all pregnant women.[5] Labour and delivery suites are the other places where pregnant women will present.

Women who are in labour without documentation of results from an HIV test during pregnancy should be counselled and screened with a rapid HIV test.[5] Immediate initiation of appropriate antiretroviral prophylaxis should be recommended on the basis of a positive rapid test result.

The major risk factor for mother-to-child transmission is maternal viral load (plasma HIV RNA) level. High plasma HIV viral load are found in cases with advanced HIV disease, a low CD4 cell count, poor adherence to antiretroviral therapy and primary infection.

Plasma HIV RNA levels may also be increased in the presence of STIs, malaria and worms. Invasive procedures during delivery (foetal scalp monitoring, vacuum extraction, episiotomy and use of forceps) and prolonged rupture of membranes should be avoided. Likewise, the risk of mother-to-child transmission is increased if infants are breastfed rather than bottlefed, especially in cases with the presence of cracked nipples or mastitis.

World Health Organization (WHO) guidelines, including the avoidance of mixed feeding, should be followed to minimise mother-to-child transmission if breastfeeding is the most appropriate feeding option for the mother and infant.[6]

**Case study 12.1**

A 17-year-old woman presents in labour with her first pregnancy with no antenatal care and decreased foetal movement for one day. Her HIV status is unknown and there are no signs of either HIV or any STI. She has regular uterine contractions and pelvic examination shows cervical dilation two centimetres with intact membranes. Ultrasonogram estimates the foetal weight of 2500 g and continuous cardiotocography shows lack of beat-to-beat variation and decelerations. An emergency caesarean section is planned.

An HIV rapid test is positive and her CD4 cell count is 420 cells/μL; an active 2700 gm male infant is delivered by caesarean section without maternal complication. The mother receives a single dose of nevirapine (2 mg/kg) and zidovudine plus lamivudine for seven days. The infant is also given a single dose of nevirapine (2 mg/kg) and zidovudine (4mg/kg) twice daily for 4 weeks.

Counselling includes disclosure of serostatus and HIV testing of her husband, who is found to be HIV negative. Contraception and condom use are discussed. She is scheduled for postpartum follow-up, cervical cancer screening and long -term follow-up.

## HIV screening in gynaecological settings

Conditions such as persistent vulvovaginal candidiasis, cervical intraepithelial neoplasia (CIN), and cervical cancer occur more frequently in women with HIV infection.[7] All STIs, particularly herpes simplex or bacterial vaginosis, enhance susceptibility to HIV. HIV testing should therefore be offered to all women presenting with the above conditions.

## HIV and cervical neoplasia

Although invasive cervical cancer is an AIDS-defining illness, evidence of an increased incidence of invasive cervical cancer as a consequence of HIV infection is inconsistent. While the association between increased rates of cervical dysplasia and cervical intraepithelial neoplasia and HIV is clear, the effect of HIV on the development and progression of these precursor lesions to invasive cervical cancer is complex and incompletely understood.

Nevertheless, several studies have found that women with HIV have a higher prevalence of human papillomavirus infection and are likely to develop persistent infection with multiple human papillomavirus types, resulting in higher incidence and prevalence of cervical intraepithelial neoplasia and increased likelihood of rapid progression to cervical cancer.[8] In addition, HIV-positive women may present with metastases (often at unusual sites) at time of diagnosis,[9] high recurrence rates after standard treatment and experience a high death rate.[10]

## Screening program for cervical neoplasia

Women with HIV should have a Pap test at their initial evaluation with a repeated screening at six months. If both results are negative, then Pap testing should be scheduled annually in those women with CD4 cell counts greater than 500/μL and every six months in those with lower CD4 cell counts.[11] Cases having abnormal cytology should be referred for appropriate diagnostic procedures.

## References


1. UNAIDS/WHO. AIDS epidemic update: December 2007. Geneva: UNAIDS and World Health Organization, 2007.

2. Working Group on Mother-to-Child Transmission of HIV. Rates of mother-to-child transmission of HIV-1 in Africa, America, and Europe: results from 13 perinatal studies. J Acquir Immune Defic Syndr Hum Retrovirol 1995;8:506–10.

3. Warszawski J, Tubiana R, Le Chenadec J, Blanche S, Teglas JP, Dollfus C, et al for the ANRS French Perinatal Cohort. Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. AIDS 2008;22:289-99.

4. Temmerman M, Quaghebeur A, Mwanyumba F, Mandaliya K. Mother-to-child HIV transmission in resource poor settings: how to improve coverage? AIDS 2003;17:1239-42.

5. Centers for Disease Control and Prevention. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. Morb Mort Wkly Rep 2006;55(No. RR-14):8-10.

6. WHO, UNICEF, UNFPA, UNAIDS. HIV transmission through breastfeeding: a review of available evidence: 2007 update. Geneva: World Health Organization, 2008:33-40

7. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. Morb Mort Wkly Rep 1993;41:1-19.

8. Schuman P, Ohmit SE, Klein RS, Duerr A, Cu-Uvin S, Jamieson DJ, et al. HIV Epidemiology Research Study (HERS) Group. Longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV) seropositive and at risk HIV-seronegative women. J Infect Dis 2003;188:128–36.

9. Zanetta G, Maneo A, Colombo A, Ragusa A, Gabriele A, Placa F, et al. HIV infection and invasive cervical carcinoma in an Italian population: the need for closer screening programmes in seropositive patients. AIDS 1995;9:909-12.

10. Maiman M, Fruchter RG, Clark M, Arrastia CD, Matthews R, Gates EJ. Cervical Cancer as an AIDS-defining illness. Obstet Gynecol 1997;89:76-80.

11. Zorrilla CD. HIV infection in women: perinatal issues and cervical cancer surveillance. Top HIV Med 2007;15:1-5.

# 13 HIV infection in injecting drug practice

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## Common presentations of HIV in injecting drug users in Asia

In several countries in Asia, the most at-risk population for human immunodeficiency virus (HIV) infection is the injecting drug user (IDU) population. The clinical presentation of HIV among IDUs does not differ significantly from that in the general population with HIV infection. Common presentations are listed in Table 13.1. However IDUs with HIV infection may also present with clinical complications of injecting drug use, which can be more common or more fulminant due to HIV-related immunosuppression.[1,2] IDUs often present with late stage HIV disease as they can be reluctant to access health services.

**Table 13.1. Common clinical conditions in injecting drug users with HIV infection[1,2,3]**

- Tuberculosis and respiratory tract infections
- Wasting
- Oral thrush
- Skin lesions
- Persistent diarrhoea
- Hepatitis B and C
- Sexually transmitted infections
- Psychiatric disorders

**Clinical conditions of injecting**

- Skin and soft tissue infections
- Local injection site reactions, hematomas and keloid scars
- Venous disease including thrombophlebitis, thrombosis and chronic venous insufficiency
- Arterial disease including aneurysm and peripheral ischaemia
- Sepsis – endocarditis, endophthalmitis and osteomyelitis

HIV counselling and testing are recommended on a regular basis (every 6 to 12 months) for all IDUs with persistent risk behaviour. Provider-initiated counselling and testing are very important when IDUs present with any of the clinical conditions in Table 13.1. Regular provider-initiated counselling and testing are particularly appropriate when there is an ongoing relationship between an IDU and a regular health provider. IDUs who test negative for HIV should receive ongoing counselling on how to avoid and prevent transmission of HIV and when to be re-tested for HIV.

## Respiratory tract infections

Respiratory tract infections are one of the most common presentations of HIV in IDUs. Respiratory illness is estimated to be 10 times more common in IDUs with HIV infection than in the general population with HIV with a 7.5 fold increased risk of bacterial pulmonary disease.[1]

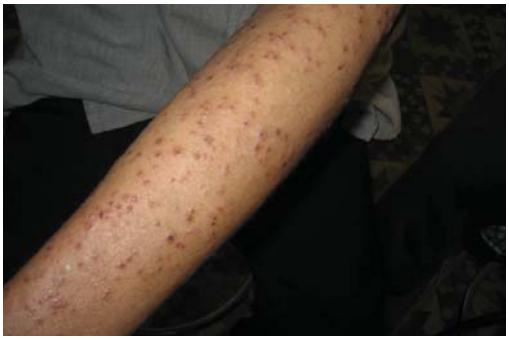
IDUs with HIV infection often present septic and unwell with an abrupt onset of fever and respiratory signs and symptoms. This presentation may be related to pulmonary tuberculosis caused by *Mycobacterium tuberculosis* and bacterial pneumonia caused by *Streptococcus pneumoniae, Haemophilus influenzae* or Gram-negative organisms such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Where the CD4 count is below 200 cells/μL, pneumocystis pneumonia related to *Pneumocystis jirovecii* should be considered in addition to rare pathogens such as *Rhodococcus equi, Cryptococcus, Penicillium, Aspergillus* and *Nocardia*.[1,2,3] IDUs with HIV infection may also present with respiratory symptoms due to *Staphylococcus aureus* septic emboli or cardiac failure secondary to bacterial endocarditis or acute respiratory distress syndrome.

Any IDU presenting with tuberculosis, bacterial pneumonia or any other respiratory conditions should be offered HIV counselling and testing. If the HIV test is positive, a CD4 test will allow better assessment of the most likely pathogen.

## Skin and soft tissue infections

Soft tissue infections (abscesses, cellulitis) including necrotising fasciitis are more common among IDUs (prevalence of up to 32% in some settings), and are related to contaminated injecting equipment, poor injecting hygiene, unsafe injecting practices and a high rate of chronic *Staphylococcus aureus* carriage which predisposes to invasive infections. Skin and skin structure infections are both more frequent and more severe in immunocompromised individuals with HIV infection.[1,2] IDUs with HIV and skin and soft tissue infections usually present with an abrupt onset of fever with erythema, pain and tenderness over the infected area.

The site of infection usually corresponds to the preferred site of injection, which is often the arm, although injecting in the leg and groin is common in the Asian and Pacific regions. IDUs with HIV infection can also present with skin lesions due to scabies, papular pruritic eruptions, herpes simplex virus (Figure 13.1), herpes zoster virus and *Penicillium marneffei* (Figure 13.2). All IDUs presenting with skin and soft tissue infections or conditions should be offered HIV counselling and testing.[1,2,3]



**Figures 13.1:** Penicillium marneffei in an injecting drug user with HIV infection

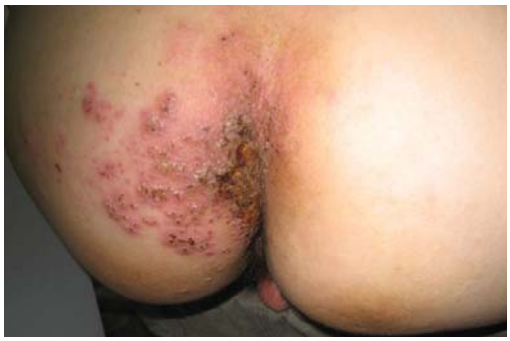


**Figure 13.2:** Herpes simplex virus in an injecting drug user with HIV infection

Photo courtesy of Binh Thanh HIV Clinic, Ho Chi Minh City and Van Don District HIV Clinic, Quang Ninh, Vietnam.

Scarring from herpes zoster in an IDU should alert a health worker to the possibility of HIV (Figure 13.3).

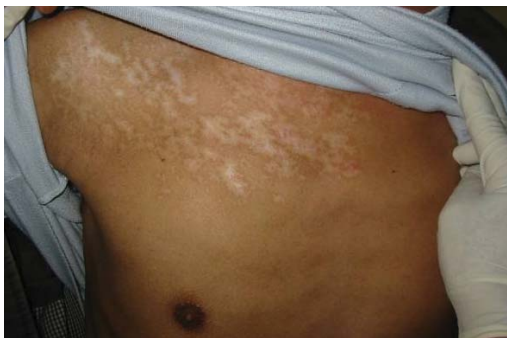


**Figure 13.3:** Scarring from herpes zoster in an injecting drug user. Photo courtesy of Van Don District Hospital HIV Outpatient Clinic, Quang Ninh, Vietnam

## Hepatitis

IDUs with HIV infection can present with a range of symptoms including fulminant acute hepatitis, end stage cirrhosis, hepatoma or asymptomatic liver disease with abnormal liver function tests (LFTs).

These may be due to HIV and any, or a combination, of the following:

- Hepatitis B virus (HBV).
- Hepatitis C virus (HCV).
- Hepatitis from sepsis, tuberculosis and other opportunistic infections (cytomegalovirus, *Mycobacterium avium* complex, *Penicillium marneffei*).
- Alcoholic hepatitis.
- Medication induced hepatitis.

IDUs with HIV are much more likely to have active HCV and HBV infection than IDUs without HIV, as both HCV and HBV are less likely to clear spontaneously in the presence of HIV. The TREAT Asia database reports that the rate of HIV-HCV or HBV co-infection in IDUs ranges from 10-90% in Asia.[4] All IDUs who have positive serology for hepatitis B and hepatitis C and all those who have abnormal LFTs of unknown aetiology should be referred for HIV counselling and HIV testing.

## Psychiatric co-morbidity in injecting drug user with HIV infection

Common clinical psychiatric presentations in IDUs include depression, anxiety disorders and drug-induced psychosis. Personality disorders and self-harming behaviours are also common.[1,2,3] HIV infection interacts with psychiatric illness in a complicated manner. There is a strong relationship between depression and HIV with depression reported at increased rates in almost all populations with HIV.

It is thought that depression is more frequent in advanced HIV disease. Mania and psychosis related to HIV encephalopathy, progressive multifocal leukoencephalopathy and HIV replication in the central nervous system have been reported.[1,2,3] It is important to note that psychiatric illnesses can manifest differently depending on the cultural setting; an understanding of the local context is very important in the clinical assessment of IDUs with mental illness.

Given the relationship between HIV, IDU and mental illness, it is recommended that all IDUs presenting with psychiatric illnesses should be referred for counselling and HIV testing.

## Infections related to complications of injecting drug use

Bacterial endocarditis is a serious life-threatening complication of injecting drug use. There is a fourfold increase in the risk of endocarditis in IDUs with HIV infection compared to those without HIV infection. The risk of endocarditis appears to be related to the level of immunosuppression and is more common in those who have CD4 cell counts less than 350 cells/μL.[1,2,3] Other infections caused by septic emboli related to injecting practices are osteomyelitis and endophthalmitis.

These conditions are also thought to be more common in IDUs with HIV infection and can present with non-specific symptoms such as pain, fever and visual loss. All IDUs presenting with unusual symptoms that may be related to infective complications of injecting should be tested for HIV.

## When and where do injecting drug users with HIV infection present

IDUs with HIV may be found in any clinical setting, in addition to drug relapse prevention programs, harm reduction outreach programs and in closed settings (prisons or voluntary/involuntary rehabilitation centres). It is important to remember that IDUs with HIV often present late and with advanced disease (Figure 13.4).

Health and allied health workers need to think of HIV when any IDU presents unwell - particularly those with fever, weight loss, cough, unusual pain and skin lesions including oral candidiasis. The value of a thoughtful and sensitive medical history and a thorough clinical examination cannot be understated in order to make a diagnosis of HIV in a timely fashion.

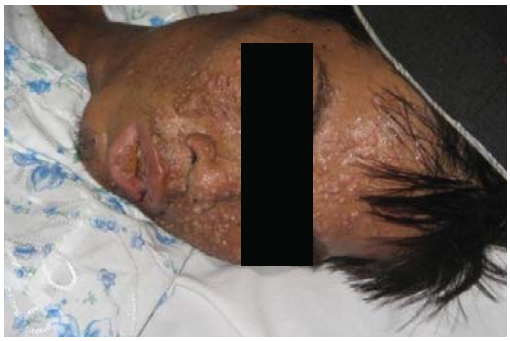


**Figure 13.4:** Late presentation of an injecting drug user with HIV infection for clinical care in Ho Chi Minh City, Vietnam. Wasting, fever and respiratory symptoms are very common.

**Case study 13.1**

Patient T is a 24-year-old man who started injecting heroin at aged 20 years and has just been released from a compulsory drug rehabilitation centre where he had been a resident for 3 years. He had been home with his family for a month when he became so unwell that they decided to take him to the district hospital. He was complaining of progressive shortness of breath, fevers which were worse in the afternoon and evenings, loss of weight and extreme fatigue. On examination in the emergency department he was febrile, dehydrated, wasted (body weight 38 kg), short of breath at rest, and he had keloid injecting scars in the groin and left cubital fossae. He had visible oral candidiasis.

**Questions to consider:**

- Could it be HIV – when and how would you do an HIV test?
- What is your differential diagnosis of shortness of breath in this man?
- What other clinical conditions do you need to think about?
- What investigations would you consider necessary?

He was admitted for inpatient care. A chest x-ray showed bilateral hilar lymphadenopathy, patchy consolidation and a right pleural effusion (Figure 13.5)

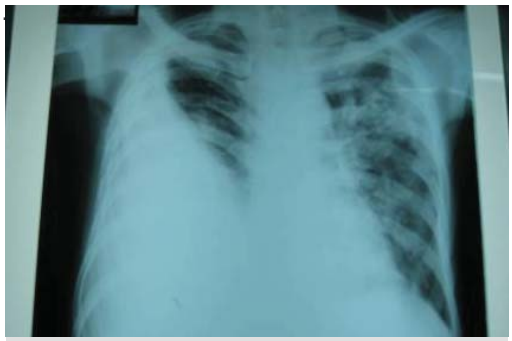


**Figure 13.5.** Chest x-ray showing bilateral hilar lymphadenopathy, patchy consolidation and a right pleural effusion. Photo courtesy of Van Don District Hospital HIV clinic, Quang Ninh, Vietnam.

He tested HIV positive on both rapid and confirmatory ELISA tests and also tested sputum positive for tuberculosis. He was hepatitis C Ab positive and hepatitis B sAg positive with an alanine aminotransferase (ALT) value of 250 U/L and an aspartate aminotransferase (AST) value of 220 U/L. He responded to treatment in hospital where he was an inpatient for six weeks. One week prior to discharge from hospital he had a CD4 count of 46 cells/μL.

**Questions to consider:**

- What is the WHO clinical stage[5] of this man?
- What is your treatment for this man and when would you start antiretroviral therapy?
- What antiretroviral therapy regime would you use?
- What other care and support measures would you consider important?

## Acknowledgments

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Dr David Jacka, WHO Vietnam, for his review and useful comments and recommendations.

# References


1. Module 2: WHO-SEARO and WPRO training modules. Treatment and Care for HIV-Positive Injecting Drug Users. Comprehensive Services for injecting drug users – participant manual. Jakarta: ASEAN Secretariat, December 2007.

   Available at: http://www.fhi.org/training/en/HIVAIDS/IDUModules/pdf/Module_2_Treatment_Carefor_HIV_positive_IDUs.pdf (Cited 19 May 2009).

2. Module 6: WHO-SEARO and WPRO training modules. Treatment and Care for HIV-Positive Injecting Drug Users. Managing ART in injecting drug users – participant manual. Jakarta: ASEAN Secretariat, December 2007.

   Available at: http://www.searo.who.int/LinkFiles/Publications_Module_6_Treatment_&_Care_for_HIV_positive_IDUs.pdf (Cited 19 May 2009).

3. O'Connor PG, Selwyn PA, Schottenfeld RS. Medical care for injection-drug users with human immunodeficiency virus infection. N Engl J Med 1994:331:450-9.

4. Zhou J, Zhang FJ, Lim PL, Dore GJ, Chen YMA on behalf of The TREAT Asia HIV Observational Database – "Hepatitis B and C virus Co-infection in the TREAT Asia HIV Observational Database" IAS 2006.

   Available at: http://www.aids2006.org/Web/TUAB0302.ppt (Cited 3 June 2009)

5. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. 2007.

   Available at: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf (Cited 18 May 2009).

# 14 Laboratory diagnosis of HIV infection

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Laboratories can reliably deliver accurate human immunodeficiency virus (HIV) diagnoses in almost all specimens, except during acute HIV infection. In addition, the diagnosis of opportunistic infections, sexually transmissible infections, haematological abnormalities, such as unexplained thrombocytopenia or histological diagnosis of cancers, such as Kaposi's sarcoma or a lymphoma, should prompt the laboratory to advise the clinician to consider HIV as a diagnosis.

## Introduction

It is well established now that 20-80% of the people in different parts of the world who have HIV infection do not know their HIV status.[1] It is therefore important to make use of every opportunity to offer to test people who are unaware of their status. Laboratories can play an important role in managing testing procedures by having clear and detailed test request protocols (e.g. provide relevant clinical information on forms), and by carefully evaluating all HIV test results according to the most up-to-date diagnostic protocols.[2]

## HIV serology

Most people develop antibodies against HIV that are detectable by standard enzyme-linked immunoassays (ELISA) within 30 days after infection, although some seroconvert later. The vast majority of people (99%) have detectable antibodies by three months after HIV infection.[3] The 'window period' is the time it takes for a person who has acquired HIV infection to react to the virus by creating HIV antibodies.

The average window period to detect seroconversion using HIV-1 antibody tests is 22 days for subtype B. Antigen testing shortens the window period to approximately 16 days and nucleic acid amplification testing (NAAT) further reduces this period to 12 days.[3] During the window period, a person with HIV infection can transmit HIV to others although their HIV infection may not be detectable with an antibody test.

All diagnostic tests have limitations. False-positive results occur when a test is reactive, but the person does not really have HIV infection. False-negative results occur when a test is non-reactive, but the person actually has HIV infection. An HIV diagnosis should be based upon the outcome of two or more tests. However, when two test results disagree (i.e. one is reactive, the other non-reactive), the finding is said to be discordant. In this case, a third test or a test using another platform (e.g. NAAT for viral load) should be performed.

### ELISA: the first generation of HIV testing

ELISA tests are usually the first HIV screening tool. A positive ELISA test result is usually observed within 3-6 weeks following infection. Very rarely, antibodies may develop up to 12 weeks after infection. Beyond the window period, ELISA tests are rarely false negative. This means if the patient has a negative test result, and is beyond the window period after the last potential exposure, the test is truly negative. An ELISA test may rarely be false positive.

False-positive ELISA results can occur in the presence of other auto-antibodies, hepatic disease, influenza vaccination and an acute viral infection, as well as from laboratory errors of procedure and specimen handling. For these reasons, positive ELISA results should always be followed by confirmatory tests.

## Western blot: the confirmatory test

The Western Blot (WB) is a confirmatory test: it is only performed if an ELISA or rapid test is positive. The WB can be positive, negative or indeterminate. If no viral bands are detected, the result is negative. If at least one viral band for each of the GAG, POL, and ENV gene-product groups is present, the result is considered positive. In certain circumstances in which a few viral bands are detected but not enough to confirm infection, the result will be considered as indeterminate.

A person who has an indeterminate result should be retested, as later tests may be more conclusive. Almost all persons with HIV infection with indeterminate Western-Blot results will develop a positive result when retested one month later; persistently indeterminate results over a period of six months suggest the results are due to cross-reaction with other antibodies and do not represent true HIV infection.

## Rapid testing

Rapid tests have become popular in resource-limited, remote or field settings for HIV diagnosis. These tests can be carried out with minimal training, and do not require expensive laboratory equipment for testing or biohazardous reagent disposal.[4] The tests also play a valuable role in situations where a test result is urgently required, such as testing of a source patient after a needle-stick injury and pregnant women in labour.

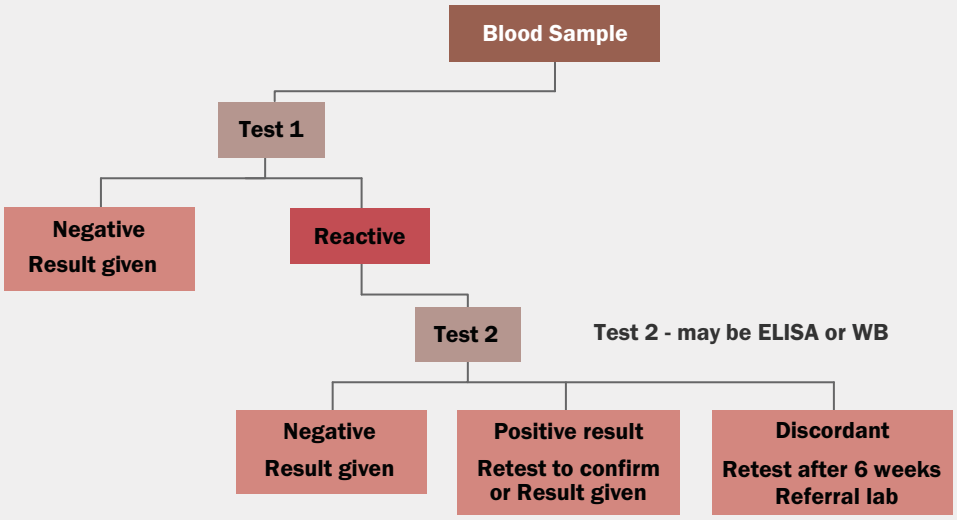
Presently non-reactive (negative) results may be reported on the result of a single test, but reactive test results must be confirmed through standard serological testing. For intrapartum women, repeat rapid testing with other test kits may be more appropriate in order to obtain a result before delivery. Currently a number of rapid screening test kits are available; four FDA-approved tests are summarised in Table 14.1.

**Table 14.1: US Food and Drug Administration (FDA)–approved rapid HIV antibody tests for HIV-1 detection[5]**

| Rapid HIV test | Specimen type | Sensitivity† | Specificity† |
|---|---|---|---|
| OraQuick® Advance Rapid HIV-1/2 | Oral fluid | 99.3% (98.4–99.7) | 99.8% (99.6–99.9) |
| Antibody | Whole blood (finger stick or venipunctures) | 99.6% (98.5–99.9) | 100% (99.7–100) |
| | Plasma | 99.6% (98.9–99.8) | 99.9% (99.6–99.9) |
| Reveal™ G-2 Rapid HIV-1 Antibody | Serum | 99.8% (99.5–100) | 99.1% (98.8–99.4) |
| | Plasma | 99.8% (99.5–100) | 98.6% (98.4–98.8) |
| Uni-Gold Recombigen® HIV | Whole blood (finger stick or venipuncture) | 100% (99.5–100) | 99.7% (99.0–100) |
| | Serum and plasma | 100% (99.5–100) | 99.8% (99.3–100) |
| Multispot HIV-1/HIV-2 Rapid | Serum | 100% (99.94–100) | 99.93% (99.79–100) |
| | Plasma | 100% (99.94–100) | 99.91% (99.77–100) |

† 95% CI
Modified from Health Research and Education Trust.
Available at http://www.hret.org/hret/programs/hivtransmrpd.html

An algorithm using rapid tests for HIV diagnosis is presented below (Figure 14.1):




Source: WHO/CDC rapid testing guidelines 2004 [6]

ELISA: enzyme-linked immunoassay
WB: Western Blot

**Figure 14.1:** Algorithm using rapid tests for HIV diagnosis

However, note that the predictive value of tests depends on prevalence of infection.Table 14.2 outlines the predictive values based on a test which has a sensitivity and specificity of 99%.

**Table 14.2: Predictive values for rapid HIV tests[6]**

| HIV prevalence | 0.1% | 1% | 5% | 10% | 30% |
|---|---|---|---|---|---|
| NPV single test | 100% | 100% | 99.9% | 99.9% | 99.6% |
| PPV single test | 9% | 50% | 84% | 92% | 98% |
| PPV two tests | 91% | 99% | 99.8% | 99.9% | 100% |

NPV: Negative Predictive Value
PPV: Positive Predictive Value

For example, in a country where the population prevalence is estimated at 1%, a test with a sensitivity and specificity of 99% would only be 50%, i.e. 50% or half the reactive tests will be false positives. Two tests are required to achieve a positive predictive value (PPV) of 99%.

## Nucleic Acid Amplification Test (NAAT): shortening window period and early infant diagnosis

NAAT is used to detect the presence of genetic material of the HIV virus. Various PCR assays have been designed to detect the highly conserved region of the HIV GAG gene. These assays are highly sensitive and meant to be used for early detection. For example, since 2001, donated blood in the USA has been screened with nucleic-acid-based tests, shortening the window period between infection and detectability of the virus genome to about 12-15 days. DNA and RNA tests for HIV may function as qualitative diagnostic assays that demonstrate infection, or quantitative detection systems that measure the level of circulating copies of HIV nucleic acid for prognostic or therapeutic monitoring (viral load tests).

Nucleic acid tests are also useful for resolution of cases where serological tests are inconclusive (indeterminate) and the diagnosis of HIV infection in newborns. Qualitative HIV DNA PCR tests detect proviral DNA that has been integrated in cellular DNA of the host. HIV antibody tests are not helpful in infants due to the persistence of maternal antibodies for up to the first 15 months of life. Peripheral blood mononuclear cells are recovered from whole blood from the patient, from which DNA is extracted and PCR is performed.

Most newborns with HIV infection are identified from birth within a 4-6 week post-partum period using HIV DNA PCR. Some newborns with the infection may not be detected at the time of birth reflecting the time of transmission which occurred from the HIV-positive mother. In utero infection is suspected when a newborn has a detectable DNA PCR result at 48 hours after birth, whereas transmission during labour and delivery or breast-feeding is detected 2-12 weeks later. Because of the importance of initiating therapy as early as possible, DNA PCR testing is recommended within the first 3 months to identify infants who would greatly benefit from treatment.

Venipuncture in children is not easy particularly if they are unwell; and the procedure requires an experienced phlebotomist. More recently the use of dried blood spots has been successfully applied to qualitative DNA PCR tests. This alternate specimen collection method is more acceptable in the form of capillary blood dried on specimen collection paper (Whatman#903), allowed to dry overnight, packaged and transported to a reference laboratory for testing (Figure 14.2). This specimen type has greatly improved access to early infant HIV DNA testing in remote resource-constrained settings.

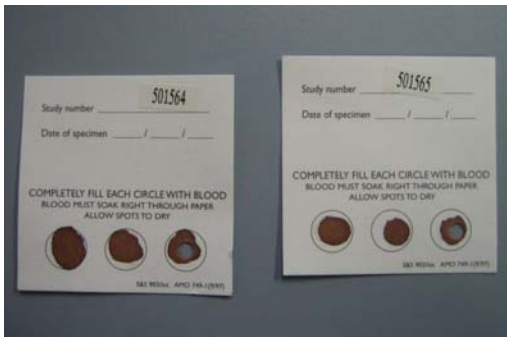



**Figure 14.2:** Dried blood spot specimens suitable for HIV DNA PCR testing of infants born to HIV-seropositive mothers.

## HIV p24 Antigen test

p24 antigen testing may be used to help diagnose early HIV infection. Levels of p24 antigen increase significantly at about one to three weeks after initial infection. It is during this time frame before HIV antibody is produced when the p24 test is useful in helping to diagnose infection. About 2-8 weeks after exposure, antibodies to HIV are produced and remain detectable in response to the infection, making the HIV antibody test the most useful assay to diagnose an infection.

# Laboratory quality assurance

Measures to ensure quality must be applied to all tasks and procedures conducted before, during and after the performance of each laboratory analytical procedure.

Inaccurate results caused by technical or transcriptional errors are preventable and an effective quality system can eliminate these errors.[4,7]

The term Quality System encompasses all quality measures related to the entire testing system (pre-analytical, analytical and post-analytical phases of testing). All steps from the correct labelling and identification, requesting of correct tests, appropriate specimen containers, appropriate transport to laboratory, correct receipt and registration procedures once the sample is received by the laboratory can influence the quality of what enters the testing process.

Once specimens enter the testing process factors such as reagents and test methods are important. Having and using appropriate quality controls, assay acceptance or rejection validity controls, worksheets and forms to minimise transcription errors, equipment calibration and performance, testing conditions such as incubation times, temperatures, humidity, power and water quality are all critical to quality output. Post analytical procedures include how results and records are managed to ensure traceability; reporting of results in a clear and unambiguous manner to ensure correct interpretation. Archiving and long-term result management may also be important.

The Quality System includes the management of both administrative and technical aspects of the laboratory. Regardless of the size or scope of the laboratory or whether in voluntary counselling and testing (VCT) clinical settings in the context of rapid tests, many of the elements of the laboratory quality system should still apply to reduce sources of error, contamination, controlled environment and traceable records and results.

**Case study 14.1**

A 28-year-old healthy male presents for HIV testing to his local VCT centre.

An initial rapid test yields a weakly reactive result (faint band on Determine® test)

This is followed by a second test from a different manufacturer, which yields a negative result.

- What is your interpretation?
- What is your further diagnostic approach?
- What do you tell the patient?

A number of possibilities need to be considered in the context of rapid tests and, particularly, performance of rapid tests in non-laboratory settings.

Any weakly reactive (note the terminology 'reactive' not 'positive') result should be interpreted with caution particularly in the absence of clinical or history risk assessment or without understanding the prevalence of HIV in the population being tested.

Conventional immunoassays (e.g. ELISA or chemiluminescent formats) involve carefully controlled reactions to optimally complex antibody - antigen test components. Reactions generally reach a steady state of equilibrium where the antibody in the patient's serum binds to the antigen in the tests to form a stable complex which is in turn detected.

Rapid tests or, more appropriately termed, short incubation tests do not reach a steady state of equilibrium and are usually read while the test is still in a dynamic stage of antibody-antigen complex reaction. Because of this, reactivity may be variable and more likely to be affected by environmental factors which are known to drive immunological reactions, such as, most commonly, temperature. Performance of rapid tests in uncontrolled environments may give rise to variable results such as ambient temperature being too high (common in tropical countries) and when the reactions are not adequately timed by the use of calibrated timing devices. Other variables may include reader interpretation, volume and type of sample applied to the test, reagent stability such as inappropriately stored tests, expiry date and variable manufacturer production batch.

The World Health Organization (WHO) recommends the use of a second test which has been evaluated and chosen to complement the first test usually of higher specificity than the screening test.

Continued over page

**Case study 14.1** (Continued)

The positive predictive value (PPV) of tests performed on individuals from populations with high HIV prevalence will be greater than that from a low prevalence population. Concordance on both screening and second test in appropriately chosen tests will greatly improve the PPV of the final test result. This scenario highlights the importance of using validated testing strategies to confirm true from false reactivity in HIV diagnostic testing. In any case, if the result of the test is unexpected or simply to confirm the initial result, a second sample of venous blood should be collected and sent for conventional HIV antibody testing in a reference laboratory.

Weakly reactive test results may be observed in early seroconversion in individuals reporting high risk exposures 3-4 weeks before testing. Seroconversion involves the development of antibodies in response to exposure to the virus. The primary care provider may be alerted to clinical evidence of acute retroviral syndrome which may include some or a number of symptoms such as fevers, non-exudative pharyngitis, adenopathy, malaise arthralgias, myalgias, headache featuring retro-orbital pain and photophobia, maculopapular erythematous rash and occasionally mild gastrointestinal symptoms.

The presence of these symptoms which may persist for up to 3 weeks may be less obvious in individuals from different racial backgrounds. In this case, the discordance in the two tests may be due to a difference in the sensitivity (limit of detection) of one test over another.

**Case study 14.2**

An infant is delivered by normal vaginal delivery to a woman given a short-course of nucleoside reverse transcriptase inhibitors (NRTIs) as prophylaxis during the third trimester of pregnancy. The mother has agreed to formula-feed her baby. She is anxious to know the HIV status of her child.

- What test(s) do you order?
- How will you advise the mother?

There are many benefits to determining the HIV status as early as possible in exposed infants. Antiretroviral therapy, adjunctive therapy and prophylaxis for opportunistic infections can be initiated and evaluated during the critical first 3-6 months. There may be opportunities for newborns to undertake routine immunisation schedules, provision of social and medical support and early monitoring of nutritional status are clear benefits.

When the newborn's serum is tested, the maternal IgG may be detected for up to 15 – 22 months. IgG has a half life of approximately 3 weeks, so maternal antibodies are clearly relatively slowly declining over many months in the infant without infection. In addition, maternal antibodies to HIV may be passively transferred to the newborn postnatally through breastfeeding. If a standard antibody is the only test available, then the infant must be continually monitored for seroreversion (tests converting from positive to negative) for up to 18 months. This seroreversion does not however exclude infection with HIV until the newborn becomes immunocompetent to produce its own antibody response.

Other laboratory techniques may be used to diagnose HIV infection in the newborn by the use of direct detection tests (e.g. HIV-1 p24 antigen serological tests and nucleic acid tests [DNA and RNA]). In countries with limited resources where nucleic acid tests are unavailable, p24 antigen assays may be the only way viraemia can be determined. HIV-p24 antigen tests only have a sensitivity of between 50-80% in the first 6 months but increase significantly after 6 months of age.

Testing for HIV infection in the newborn by molecular tests is recommended at 48 hours. In many resource-limited settings, breastfeeding is recommended even in HIV-positive mothers as the risk of morbidity and mortality from bottle feeding outweighs the risk of HIV transmission from breastfeeding. Therefore children must continue to be re-assessed for their HIV status until they are weaned. The use of dried blood spots may be useful in improving access to nucleic acid tests in resource-limited and remote settings as previously discussed.

# References


1. Marks G Crepaz N, Senterfitt JW, Janssen RS. Meta-Analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. J Acquir Immune Defic Syndr 2005;39(4):446-53.

2. Ridderhof JC, van Deun A, Kam KM, Narayanan PR, Aziz MA. Roles of laboratories and laboratory systems in effective tuberculosis programmes. Bull World Health Organ 2007;85(5):354-9.

3. Dodd R, Kurt Roth W, Ashford P, Dax EM, Vyas G. Transfusion medicine and safety. Biologicals 2009;37(2):62-70.

4. Constantine NT, Saville RD, Dax EM. Retroviral testing and quality assurance: essentials for laboratory diagnosis. Ann Arbor, MI: Malloy Publishers, 2005.

5. Chakraborty P. A Textbook of Microbiology. 2nd edition. P New Central Book Agency India, 2006.

6. World Health Organization (WHO) and UNAIDS. HIV Assays: Operational characteristics (Phase 1). Report 14: Simple/rapid tests 2004.

   Available at: http://www.who.int/diagnostics_laboratory/publications/hiv_assays_rep_14.pdf (Last accessed 24 September 2009).

7. International Organization for Standardization. ISO15189:2007. Medical laboratories: particular requirements for quality and competence. 2007.

# 15 Counselling and testing for HIV

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## Introduction

If you, as a heath care provider, suspect that a patient has human immunodeficiency virus (HIV), then HIV testing should be considered. In this chapter there is information on what is required to perform an HIV test. HIV testing must not be done without INFORMED CONSENT of the patient and there are several approaches as to how this can be facilitated.

HIV testing should always be conducted with pre test counselling and followed by post test counselling irrespective if the result is positive or negative. Counselling prior to and after an HIV test has many benefits including:

- providing patients with key information to make their own decision about whether to have the test
- assisting in reducing stigma and discrimination by providing factual information and increasing awareness about HIV and acquired immunodeficiency syndrome (AIDS)
- assisting the health care provider and patient to ascertain the patient's level of risk of HIV
- enabling the health care provider and patient to discuss and identify the patient's coping mechanisms while waiting for the test and the result
- promoting behaviour change to minimise HIV risk in the future for those testing negative or positive.[1,2]

## Essential aspects of HIV counselling and testing

### The three Cs of HIV testing

Recognised in the UNAIDS/WHO policy statement on HIV testing, HIV testing must be conducted under the following principles:[3]

The process and results must be:

- **CONFIDENTIAL**
- Accompanied by pre test and post test **COUNSELLING**
- Only conducted with informed **CONSENT**, meaning that it is both informed and voluntary.

### Confidentiality

Any HIV test must be confidential. The counselling session prior to obtaining informed consent should be provided in a confidential situation, preferably in a private room and one-to-one. If the patient is accompanied by a support person, then you could ask if your patient would like to have a private discussion or could offer for the patient to return at a later time to take the test independently.

Wherever possible, the test itself should be coded and not labelled with the patient's name. This de-identification is especially important in small communities where other health facility staff, such as laboratory technicians, may recognise the patient's name. This procedure should be discussed with the patient to ensure them of confidentiality.

The results must be kept confidential and, ideally, the same health care provider who provided the initial counselling should also provide the test results. The patient should be informed that the test result will be kept confidential by health care providers and the health facility, and that no one else will be informed of the HIV results unless the patient consents or, more importantly, chooses to disclose his/her status independently.

## Accompanied by counselling and factual information

All HIV testing should be accompanied by counselling, giving of factual HIV information, and a personal risk assessment. Providing the client with information and facilitating discussion about HIV provides an opportunity for learning, correcting misinformation, assisting the patient in identifying personal risks and coping strategies in preparation for the result. It also provides an opportune environment to promote behaviour change, and in turn, normalises the testing process that assists in decreasing stigma and discrimination.

Please see the boxes below regarding the information that should be discussed prior to obtaining informed consent and when delivering HIV test results.

## Informed consent

For patients to provide informed consent prior to HIV testing, they must be provided with HIV test counselling and information so that they have an understanding of the implications of the HIV test and the course of events that testing could set in motion.

It does not matter if the results are positive or negative, each person should be equipped to make the decision for themselves at that time, voluntarily, free from any form of overt or implied coercion.

Throughout Asia and the Pacific regions, there are different requirements for obtaining consent. In some cases consent must be provided in writing while in others verbal consent is considered adequate to proceed with testing. If you are unsure as to what procedure should be followed in your health facility, please consult with an HIV specialist or another facility that has more experience with HIV counselling and testing.

## Voluntary

All HIV testing must be voluntary, which means that a patient has the right to decide, after counselling, to be tested or not. If patients are undecided, they should be informed that they can return at any time when they are prepared to take an HIV test.

This type of testing is called “opt-in” testing, that is, the patient opts to have an HIV test based on the advice and decision made during pre test counselling.

There is also another type of testing called “opt-out” testing; this means that the patient will be tested unless they choose to specifically decline a test. This type of testing still requires the health care worker to inform the client about the HIV test and provide an opportunity to decline.

Patients have the right to decline an HIV test. They should not be tested for HIV against their will, without their knowledge, without adequate information to decide whether to consent, or without arrangements to receive their test results in a post test counselling session.[4,5]

At no time is it acceptable to coerce or perform mandatory testing. It is acknowledged however, that in some institutions and health facilities across the Asia and the Pacific Regions that this does occur.

## Human rights-based approach

There is also an ethical and human rights approach to HIV counselling and testing. Due to the potential for stigma and discrimination that a patient may face just in having the test performed, it is important to provide the patient with appropriate information with which to make an informed decision.

**The human rights-approach[6]**

- Right to information
- Right to give informed consent after full disclosure of relevant information
- Right to respect for cultural and religious beliefs
- Right to know to whom the result will be disclosed
- Right to treatment even if the test is refused

# Issues of access to counselling and testing

## Attitude of the health care provider

Health care providers need to understand the effect that their own attitudes and beliefs have on the patient and the HIV counselling and testing experience. The atmosphere created by the health care provider for the pre test counselling session needs to be one of respect and mutual positive regard, remembering that the patient is the authority on his or her life and lifestyle and not the health care provider.

It is also important for the health care provider to have an understanding of cultural, social and religious factors that influence the interaction with the patient and also the implications about how people with HIV are perceived within their broader social networks.

## Cultural, social and religious issues

Throughout the Asian and Pacific regions, within countries and in small communities, there are many different cultural, social and religious beliefs that affect how HIV is perceived and ultimately how people with HIV and their families and friends are viewed and treated. HIV counselling and testing has to be tailored to the patient. Some common examples of how social, religious and cultural issues affect HIV are:

- Discussion of sexuality is often taboo and patients may not be aware of even basic facts about sexuality, gender and sexual health; hence, there is an increased need for simple factual information.

- Superstitions and personal beliefs may also influence commonly held norms or activities; myths need expounding by giving factual information in a sensitive manner. For example, it is a common belief in the Pacific that it is unsafe to have sex when pregnant so men may go to sex workers and come back to their wives after the birth and possibly transmit HIV to mother and child while she is breastfeeding.

- Societal attitudes and beliefs about men who have sex with men, sex work, sex outside of marriage and injecting drug use are often discriminatory; members of these groups are usually stigmatised, marginalised and less likely to seek access to health services. Testing services for these most-at-risk groups need to be easily accessible, so that clients are safe from physical or psychological harm. This harm may occur through discriminatory practices or attitudes from the service or through the community, such as harassment from police, or discriminatory groups that may target people using the service.

## Patients can decline a test

Patients, regardless of how ill they may be or how important it would be to confirm an HIV diagnosis, have the right to decline a test in any situation. The decision to decline a test may not be necessarily a wrong or bad decision and should not be used against a patient.

Patients may decline a test because they are concerned about confidentiality aspects of the service or location; they may have a family member present and prefer them not to know about the test, or they may not feel comfortable in having a test at that time. Others may be afraid to know their status. No matter what reason is given, a patient should make their own decision about having a test. If patients decline a test, the health care provider should inform them:

- that they can return at any time for further information and or testing
- of other health facilities that can offer HIV counselling and testing services
- of information that can be used in prevention and risk reduction for that individual
- that declining the test does not affect any other health service provision.[3]

While it may seem that the time spent discussing an HIV test was wasted, if done properly, it has equipped patients with key information about HIV and prevention of transmission, the ability to consider their own behaviours and could facilitate behaviour change, especially if a personal risk assessment has been facilitated.

# Pre and post test counselling

There are many possible topics that should be included in an HIV pre or post test counselling session. However, it is important to tailor the discussion to the patient. Below is a list of items that make up the essential standards for HIV testing and counselling services in the Pacific region.[7]

## Pre test counselling

- **Confidentiality:** The patient's legal rights around confidentiality are outlined and counsellors explain how confidentiality will be maintained at the HIV testing and counselling service.
- **Information about HIV:** Basic information regarding HIV infection is provided, including how it can and cannot be transmitted, disease progression, opportunistic infections and treatments available.
- **Risk assessment:** A comprehensive risk assessment is conducted to identify possible risks, and safer behaviours are discussed.
- **Transmission prevention:** Information about the prevention of HIV transmission is provided and, where necessary, problem-solving strategies around an individual patient's barriers to practising safer behaviours are discussed.
- **Window period:** An explanation is given of the window period of the HIV tests used and the limitations this places on the accuracy of the test results.
- **Reasons for testing:** The patient's motivation for attending for testing and counselling is assessed. This may expose previous risk incidents or highlight misconceptions about risk behaviours that need to be addressed.
- **Advantages and disadvantages of testing:** The advantages and disadvantages of testing are explained so the patient is capable of making an informed decision about whether or not to proceed with testing.
- **Right to decline:** The patient is made aware of his or her right to refuse to test or to withdraw from the testing procedure at any time.
- **Declining does not impact on service access:** Patients are informed that their decision regarding testing will not affect their rights to access other services within the health facility, with the exception of those services which rely on knowledge of a patient's HIV status, such as access to antiretroviral medications.
- **Follow-up services:** Patients are advised about services that would be available if they were to test positive (reactive).
- **Disclosure if positive (reactive):** Patients are encouraged to think about who would be their key supports in the event of a positive result. It is advisable to consider this aspect as part of pre test counselling as the patient may be emotionally overwrought and unable to think clearly about this issue during post test counselling.
- **Opportunity for questions:** The patient is provided with ample opportunity to ask questions.

At the completion of pre test counselling, the patient should be provided with relevant information education communication (IEC) materials and information on the process for obtaining results.

## Post test counselling: negative result

- **Explanation of result:** It is explained to the patient that a negative test result indicates that the patient has not developed antibodies against the virus which means that the patient has not contracted HIV.
- **Window period:** The counsellor should ensure that the patient understands what the window period is, how this might impact on the interpretation of negative test results and whether a follow-up test is recommended.

Continued over page

**Post test counselling: negative result (Continued)**

- **Transmission prevention:** Information is provided to the patient about protection from infection in the future, including the use of condoms and safer sexual practices.
- **Condom provision:** Education is provided about the importance of condom use in transmission prevention and the patient is offered condoms either free of charge, or at a subsidised cost.
- **Referral if necessary:** Information is provided regarding services available to the patient if additional support (e.g. social support networks) is needed. In the event that the HIV test counsellor feels the patient is in need of further counselling or specialist assistance, the patient should be referred to other professionals as required.
- **Opportunity for questions:** The patient is provided with ample opportunity to ask questions.

**Post test counselling: positive result**

- **Explanation of result:** The result is explained clearly and the patient given time to consider it.
- **Assistance to express and cope with emotions:** Patients are encouraged to explore what they may be thinking and feeling about their result.
- **Identification of immediate concerns and support person(s):** Patients' immediate concerns about their results are discussed and strategies discussed in pre test counselling, including identifying a support person, are reviewed.
- **Advice about follow-up services and referral:** Information is provided to the patient regarding services available and how to access these services (e.g. medical review for treatment and antiretroviral therapy, social support networks and ongoing counselling).
- **Transmission prevention:** Patients are educated about how to prevent transmission of HIV and to protect themselves from other types of infection in the future.
- **Condom provision:** The patient is educated about the importance of condom use in transmission prevention and offered condoms either free of charge, or at a subsidised cost.
- **Preventive health measures:** Patients are educated about steps that they may take to improve their health and well-being, e.g. healthy diet, reducing stress, quitting smoking, regular medical monitoring and practising safer sex.
- **Discussion of disclosure:** Patients are encouraged to consider how they may disclose to their sexual partner and key supports. The advantages and disadvantages of patients disclosing their status should also be reviewed and discussed and how they might react if their confidentiality is breached.
- **Opportunity for questions:** The patient is provided with ample opportunity to ask questions.

# The HIV test

There are many different types of HIV tests that can be preformed. Please refer to the Chapter on Microbiology Laboratory Clues for HIV Diagnosis for further information. However, there are several issues that need to be raised with the patient during pre test counselling and again at post test counselling to ensure that the patient understands the HIV test result.

## The window period

Currently, most tests can only detect HIV antibodies when they reach a certain level in the blood. It may take up to three months from the time of infection for this level to occur. This does not mean that there is an absence of the virus in the blood, but that our current technology is unable to detect the virus.

This means that a person with HIV infection could pass on the virus even if the blood test is negative. The only definite way to be absolutely sure of negative status is to be tested, to use preventive measures and to engage in no-risk behaviour for three months, and then to be retested.

## Indeterminate test result

When an HIV test is performed, it may result in an indeterminate test result, which means it is unclear whether it is reactive or not. This result can be due to factors with the test itself, contamination of the sample or it could be that the patient's body is beginning to make antibodies at the very early stages of infection.[8] Usually this result will mean that the patient will need to be recalled for further testing to ensure an accurate result.

## Confirmatory testing

Depending on which HIV test is available and the national guidelines that your health facility uses, in the event of a reactive test, confirmatory testing needs to occur. In some regions after an initial test is positive, further blood is taken and sent to a reference laboratory for confirmation of a positive result. The reason to confirm an HIV test is to ensure accuracy.

The type of testing conducted in your health care facility should be explained to the patient prior to the HIV test.

## Positive test result

If, after confirmatory testing, the result is positive, then the patient is said to have HIV infection (to be HIV positive), but this does not necessarily mean that the patient has AIDS.[8] Patients should be informed of their result as soon as possible. An HIV test and the result should be kept confidential. Only patients themselves have the right to decide to whom and when they will disclose their result.

Further testing, psychosocial and medical support should be discussed with the patient as should appropriate referrals. It is the patients' decision if they are to follow-up with a referral, and confidentiality should be maintained. It is not appropriate to forward patient information to a referral agency without the patient's permission or knowledge.

## Negative test result

A negative HIV result means that HIV antibodies have not been detected in the blood. A negative HIV test can mean either that the patient does not have HIV infection or that he or she is in the window period (see above) and should be retested if appropriate.[9]

## Contact tracing

Contact tracing is when health care providers or health facilities attempt to identify sexual contacts of the person who has been newly diagnosed with HIV, in order to refer them to testing. It is not mandatory and throughout the region it is conducted differently.

If contact tracing is agreed to, then a discussion about the procedures should be held with the patient, however, contact tracing should be carried out by experienced health care providers and a referral for psychosocial and medical support for the contact person should be made to an HIV service. If you are unsure of the contact tracing procedures, you should consult with a specialist HIV service. In the Pacific region for example, core HIV teams can be consulted.

**Key points**

- HIV counselling and testing must be voluntary and with informed consent
- A patient has the right to decline a test
- Maintaining confidentiality throughout the counselling and testing process should be of the highest priority.
- Health care providers can seek advice from peers or specialist services if assistance is required, especially for communicating an HIV-positive result and when referring a patient with HIV to an appropriate facility for further care and support.

# References


1. Coates TJ, Kamenga MC, Balmer D, Sangiwa G, Furlonge C, The voluntary HIV-1 counselling and testing efficacy study: a randomized controlled trial in three developing countries. AIDS Research Institute, Center for AIDS Prevention Studies, University of California, San Francisco. June 2000.

   Available at: http://www.caps.ucsf.edu/pubs/reports/pdf/VCTS2C.pdf (Cited 17 June 2009).

2. Denison JA, O'Reilly KR, Schmid GP, Kennedy CE, Sweat MD. HIV voluntary counselling and testing and behavioural risk reduction in developing countries: a meta-analysis, 1990-2005. AIDS Behav 2008;12:363-73.

3. UNAIDS/WHO Policy Statement on HIV testing, June 2004.

   Available at: http://data.unaids.org/una-docs/hivtestingpolicy_en.pdf (Cited 21 June 2009).

4. WHO/UNAIDS. Guidance on provider-initiated HIV testing and counselling in health facilities, May 2007.

   Available at: http://whqlibdoc.who.int/publications/2007/9789241595568_eng.pdf (Cited 12 June 2009).

5. WHO/UNAIDS. Provider initiated HIV testing and counselling in health facilities.

   Available at: http://www.who.int/hiv/topics/vct/PITC/en/index.html (Cited 12 June 2009).

6. Pacific Counselling and Social Services, Basic Counselling Skills for work in the HIV and other STI's Field, Lautoka, Fiji, (Unpublished) June 2009. To obtain a copy of the training manual please contact PC&SS at training.service @pcss.com.fj

7. Secretariat of the Pacific Community. A Guide to Evaluating HIV Testing and Counselling Services in the Pacific Island Countries and Territories (PICTs) using Minimum Standards, New Caledonia, SPC.

   Available at: http://www.spc.int/hiv/downloads/prevention-and-control-meeting-may-09/ as PICTs HIV TC Guide (5) Pre pilot Cited 17 June 2009.

8. Family Health International. VCT Toolkit. HIV Voluntary counselling and testing: Skills training curriculum. Facilitator's guide. Family Health International, January 2005.

   Available at: http://www.fhi.org/en/HIVAIDS/pub/guide/vcttrain.htm Cited 17 June 2009.

9. Finger W, Fischer S, editors. HIV counselling and testing for youth: A manual for providers. Family Health International, USA, 2007:42.

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