Hepatic disease in patients with acquired immunodeficiency syndrome (AIDS)

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SUMMARY

The acquired immunodeficiency syndrome is now the leading cause of death in the world. Liver involvement in opportunistic infections and neoplasms affecting patients with human immunodeficiency disease syndrome are common. Many of these patients also take many medicines and toxins that are potentially harmful to the liver. This is an overview on the aetiology and possible diagnostic guide to determine liver involvement in patients with HIV infection. A literature review was performed on major published series on the liver and HIV infection between 1985 and 1999, both years inclusive. Data and opinions from 5 general reviews and 31 original articles from MEDLINE on liver disease in patients with HIV infection regarding aetiology, pathology, presentation and patient evaluation are summarised. The liver is frequently affected in patients with AIDS. The majority of the patients have hepatomegaly and abnormal liver enzymes secondary to involvement with opportunities infections, AIDS associated neoplasms and drug therapy. Most of the infections reach the liver by lymphohaematogeneous spread from other sites in the body. Methodical approach in patient evaluation is therefore essential for prompt diagnosis and treatment to minimise morbidity and early mortality.

[Afr J Health Sci 2004; 11: 78-86]

Introduction

The acquired immunodeficiency syndrome is now the leading cause of death in the world. By the end of 2003 it is estimated that 34 to 46 million people are living with HIV infection worldwide and had been infected by the human immunodeficiency virus (HIV), of these, 25 to 28.2 million are in sub-Sahara Africa. Most affected is the southern part of the continent [1]. After infection with HIV, patients become susceptible to a variety of intrahepatic infections and malignancies as their cell immune status declines [2,3]. Liver disease in these patients presents in many different ways including fever, right upper quadrant abdominal pain and hepatomegaly. Up to 93 % of patients with AIDS have abnormal albumin and globulin levels [4] and up to 90% have impaired liver associated enzymes at presentation [5, 6]. When the liver is examined histologically, abnormalities are almost uniformly seen in patients with AIDS. Every physician caring for patients with AIDS therefore requires a methodical approach in evaluating and treating AIDS patients with hepatobiliary disease in order to optimize the use of the scanty resources available in the most affected parts of the world for maximum patient gain, to reduce morbidity and mortality. The aetiology of liver disease in AIDS patients may be divided into viral, bacterial, fungal, protozoal, parasitic, mass lesions, neoplasms, toxin and drugs as shown in the table in appendix 1.

Viral hepatitis

Hepatocellular necrosis is not an uncommon finding in patients with AIDS. The majority of the cases are due to viral pathogens and use of hepatotoxic drugs. Chronic viral hepatitis is prevalent in patients with HIV infection and may negatively modify their morbidity and mortality. Hepatitis B virus remains the commonest cause of chronic hepatitis and given the shared epidemiologic risks of transmission, namely high risk sexual behavoiur and exposure to infected blood products, it is not surprising that up to 95 % of the patients with AIDS have serological markers of past and present Hepatitis B virus infection and 10 – 15 % are chronic carriers for hepatitis B surface antigen (HBsAg) [4, 7,8]. However, if HIV infected patients acquire HBV infection when their immune function is already low; HBsAg carrier rate is high (20-80%) [10,11,12].

After resolution of acute HBV infection, patients with HIV infection may suffer reactivation of quiescent HBV infection, which is related to progressive decline in cell mediated and humoral immunity. Although the HB virus replicates with greater frequency as evidenced by higher DNA polymerase levels and hepatocyte hepatitis e antigen (HbeAg), transaminase levels and histologic damage to the hepatocytes remain unremarkable [7, 13]. This correlates with the degree of immunosuppression. CD4 lymphocytes play an essential role in host immune response to hepatocytes infected with HBV by stimulation of CD8 lymphocyte cell activity, which results in elimination of infected hepatocytes [14]. As CD4 lymphocyte depletion progresses in HIV disease there may be less immunologic damage to infected hepatocytes and HBV replication may proceed unrestricted. Progression to cirrhosisi is unusual [1,5]. Both HIV and HBV infect lymphocytes and hepatocytes. The HBV transactivation protein x is capable of increasing HIV replication both in vitro and in vivo suggesting that coinfection by HBV and HIV may result in activation of latent HIV and act as a co-factor in disease progression. Elevated levels of cytokines and depressed interferon levels because of HBV infection may enhance HIV multiplication as well [15]. HBV may also enhance the risk of HIV transmission [15]. Epidemiologic studies however do not suggest that HBV/HIV coinfection significantly influences the progression of HIV infection [17]. Hepatitis delta virus (HDV), a defective RNA virus, may coinfect with HBV or superinfect patients with HBsAg carrier status. Serological testing for immunoglobulin G (IgG) or 1 gm anti HDV may underestimate HDV infection due to defective antibody production in patients with AIDS [18]. HDV is directly cytopathic on hepatocytes and infection in HBsAg positive patients is associated with severe chronic progressive liver disease and more fulminant than HBV alone. HIV positive patients are also prone to disease reactivation and the ensuing hepatitis more aggressive histologically and progression to cirrhosis is common.

Hepatitis C virus (HCV), a flavi-virus like RNA virus, is predominantly transmitted via parenteral routes. Its prevalence in HIV seropositive patients varies between 1-90% [4,8,19,20]. The role of heterosexual transmission of HCV, however, appears to be small. HCV is known to be directly cytopathic to hepatocytes and cell mediated immunity appears to be important in its control. HIV induced immunosuppression may therefore favour increased HCV replication, higher circulating HCV RNA level and abbreviated progression to chronic liver disease. Some studies suggest this is the case [21] and some contradict this [8]. However, patients with HIV, HCV and HBV may have a greater risk of death from liver failure [22]. Individuals with HIV may become infected with multiple strains of HCV, and over time, more virulent strains may predominate HCV infection and induce CD4 lympocyte stimulation, which may stimulate HIV replication.

Cytomegalovirus (CMV), a common herpes virus, often affects the liver as well. Although CMV infection of the liver is usually subclinical, patients may present with fever, malaise, weight loss and hepatomegaly as well as with mild elevation of transaminases, alkaline phosphatase

and gamma glutamyl transferase. CMV is usually diagnosed on histology where mild hepatocellular necrosis associated with portal and periportal mononuclear infiltrate is observed and infected cells contain characteristic large intranuclear and small cytoplasmic inclusions, The nuclear inclusions may be surrounded by a halo forming the characteristic owl's eye appearance. Like HBV, HIV induced immune dysfunction tends to favour unrestricted CMV multiplication and hepatocytes damage. CMV infection may also present as mass lesions simulating neoplasia or granuloma. When present, CMV tends to be widespread. Herpes simplex virus (HSV) hepatitis in AIDS usually occurs in patients with extensive herpetic ulcerations elsewhere. AIDS patients with HSV hepatitis usually present with marked elevation of aminotransferases indicative of marked hepatocellular necrosis, which is often associated with coagulopathy, encephalopathy and shock [22]. On histology, hepatocytes contain Cowdry type A intracellular inclusion bodies – distinguished from CMV by immunostaining. Other human herpes viruses namely herpes virus type 6, Varicella zoster and Epstein-Barr virus as well as adenovirus may cause hepatocellular necrosis rarely leading to death.

The liver contains the largest population of tissue macrophages, Kupffer cells. Kupffer cells and sinusoidal endothelial cells have $CD4^+$ receptors making them potential targets of HIV infections [22]. In fact, immunoreactivity for HIV-1 antigens can be shown in 80% of liver biopsy specimens of patients with AIDS [21]. Biopsied liver tissue has revealed HIV P24 antigen in these cells. However, HIV infection results in little Kupffer and endothelial cytolysis or alteration of phagocytic or synthetic functions. These cells represent a physical barrier to HIV
preventing infection of the underlying hepatocytes. Despite this barrier HIV-RNA has been demonstrated in hepatocytes in patients with AIDS. The impact of these changes on liver function, morbidity and mortality remain unclear.

Bacterial causes

AIDS patients are at increased risk of developing hepatic tuberculosis. Extra pulmonary mycobacterium tuberculosis infection is seen in over 60% of AIDS patients with lung disease. From previous studies, between 3 and 7.5% of patients with extra pulmonary tuberculosis had liver involvement [24,25]. Patients present with fever, night sweats, weight loss, anorexia, lymphadenopathy and hepatomegaly. Mycobacteruim tuberculosis (TB) infection in AIDS patients usually occurs early in HIV disease and granuloma tend to form leading to patchy intraheptatic cholestasis characterized by markedly elevated alkaline phosphatase and mildly elevated bilirubin and aminotransferases. Ultrasound examination of the liver may mimic hepatic neoplastic metastases. The granulomas tend to be well formed with less tissue load of acid fast bacilli compared to mycobacterium avium complex (MAC). Unfortunately, the histologic appearance is seldom helpful in distinguishing these agents making their culture necessary for differentiation. The atypical mycobacteria M. xenopi, M. geranese and M. kansasii, may produce liver disease similar to that caused by mycobacterium tuberculosis.

In contrast to M. tuberculosis, MAC affects patients with more advanced HIV disease and often with previous history of multiple opportunistic infections. It is found in 10-30% of liver biopsy specimens in patients with AIDS and results in granulomatous inflammation with poorly formed granulomas. Patients characteristically present with nausea, diarrhoea, abdominal pain and hepatomegaly. Ultrasound examination reveals diffusely hyperechoic granulomas, which are composed of foamy histocytes with paucity of other cells and no caseating necrosis but acid fast bacilli (AFB) are found within and around the granulomas. In advanced HIV disease, granulomas may totally be absent and AFBs may be seen within Kupffer cells. Due to the non-specific nature of hepatic granulomas, Ziehl-Neelson stain must be performed on liver biopsy specimens to identify the causative organisms. Culture may be necessary to exclude the diagnosis of mycobacteria in the absence of AFBs on histology.

Protozoal infections

Entamoeba histolytica typically presents with amoebic liver abscess. When this occurs in patients with immunodeficiency, it is usually more aggressive and commonly presents with fever, tender hepatomegaly and jaundice. Investigation of choice is abdominal ultrasound. However, indirect haemagglutination test, complement fixation test, latex agglutination and enzyme immunoassay serological tests are usually positive as well.

Pneumocystis carinii, a protozoa that commonly involves the lungs may spread to involve the liver especially in patients receiving aerosolized pentamidine for prophylaxis of pneumonia. Hepatic involvement with penumocystis carinnii usually leads to granuloma that may undergo calcification [27] best seen on abdominal CT scan and plain radiography. Patients present with abdominal pain and variable elevations of aminotransferases and alkaline phosphatase. Liver biopsy shows foamy nodules that are diffuse, periportal and contain numerous pneumocystis cysts, best demonstrated using methamine-silver stain. Inflammatory reaction is typically minimal. Toxoplasma gondii may be spread via blood to the liver. It also leads to granuloma formation. Its diagnosis is by histology and recently polymerase chain reaction (PCR) analysis of liver biopsy material has been found useful [28].

Other rare protozoal liver infections include crytosporidium parvum microsporidia and reactivated leishmania donovani. Cryptosporidium (and CMV) may cause interlobular and septal cholangitis identical to primary sclerosing cholangitis.

Fungal infections

Before the emergence of AIDS, fungal infection of the liver was rare. However, as immunosuppression progresses, fungal lymphohaematogenous spread increases. Hepatic fungal infection usually leads to minimal inflammatory granulomatous response and is often asymptomatic except for fever and right hypochondrial pain. Laboratory investigations usually reveal elevated alkaline phosphatase and variable bilirubin response. Most patients often
have enlarged abdominal lymph nodes. Abdominal ultrasound and CT scan are therefore very useful in patient evaluation. The common fungal pathogens include crytococcus neoformans, histoplasma capsulatum, candida species that includes candida albicans, C. glabrata, C. tropicalis and C. krusei, coccidioides immitis and rarely aspergiluss species and sporothrix schenkii. Crytoccocal liver involvement occurs in 19 % of patients with disease outside the central nervous system [2]. Symptoms related to the nervous and respiratory systems, however, predominant the clinical picture. Occasionally, cryptococcal fungal infection may lead to abscess formation. Histoplasma involves the liver in 16 % of infected patients [6]. Fulminant disease presenting with disseminated intravascular coagulopahty, multisystem organ failure and cardiovascular collapse can occur. Silver staining of biopsy material reveals yeast with budding forms and detection of its polysaccharide antigen in blood supports the histological diagnoses.

Candida albicans presents like histoplasma capsulatum and silver staining demonstrates the yeast forms. When response to azole antifungal agents is poor, other candida species including C.glabrata, C. tropicalis and C. krusei, should be considered. Coccidiodes immitis infection usually involves the lungs but liver spread could occur. Diagnosis is by histology and tube precipitin or complement fixation tests.

Parastic infections

Liver parenchyma involvement with schistosomiasis [29] and visceral leishmaniasis may occur in patients with AIDS. Stronglyloides species (*S. stercoralis* and fuellerboni) may also cause parenchyma liver disease. This is particularly so when there is hyper-infection associated with profound immunosuppression [31].

Mass lesions

Kaposi's Sarcoma (KS), the most common hepatic neoplasm seen in patients with AIDS, is caused by Herpes virus type 8. About one third of patients with cutaneous KS have hepatic

involvement, although isolated hepatic KS can occur [2,32]. Kaposi's Sarcoma tends to originate in the capsular, hilar and portal areas and invades the parenchyma from these sites. Patients present with nigh hypochodrial pain with associated tender hepatomegaly. Live enzymes show a predominant obstructive picture with bilirubin levels within normal limits. Diagnosis is by liver ultrasound when multiple small hyperechoic masses with contrast enhancement on abdominal CT scan are found. Histology shows spindle shaped cells of vascular endothelial origin typical of KS but percutaneous liver biopsy would be a relatively unsafe procedure because of the vascular origin of the neoplasm.

Non-Hodgkins lymphoma (NHL) in patients with AIDS commonly involves extranodal sites with the liver representing the most commonly affected abdominal organ. The lymphoma is typically B-cell type of the high grade variety. Hepatic involvements has been reported in 14% of patients with lymphoma elsewhere and in 29% of patients with intra abdominal involvement [33,34]. Primary hepatic lymphoma commonly presents with B symptoms including night sweats, progressive weight loss and fever similar to those of opportunistic infections, especially tuberculosis. As the tumor grows, tender hepatomegaly becomes evident and liver enzymes show a predominant obstructive picture with markedly elevated alkaline phosphatase. Ultrasound shows nodular masses. Computerised tomography scan of the abdomen is particularly useful due to contrast enhancement of tumour margins and may demonstrate the involvement of abdominal lymph nodes [33]. Extra hepatic obstructive jaundice may follow portal and peripancreatic lymph node involvement. Peliosis hepatis, ectatic blood-filled endothelial cell lined channels, may also cause intrahepatic biliary obstruction. These lesions, caused by Bartonella henselae and generally found in severely immunosuppressed patients, are associated with fibromyxoid stroma containing few inflammatory cells, capillaries and clumps of bacilli and are best diagnosed by liver histology supported by indirect immunoflourescent testing. Peliosis hepatis with blood sequestration may lead to transfusion unresponsive anaemia and disseminated intravascular coagulopathy [35]. Peliosis hepatis may be found in organ transplant patients on immunosuppressive therapy as well.

Drugs and toxins

Patients with HIV infection often need medication with known hepatotoxic potential. Potentially hepatotoxic drugs often required by patients with AIDS may be grouped into those predominantly causing hepatocellular damage, those predominantly causing cholestatic and those causing a combination of the two are as shown in appendix ii. This list is by no means exhaustive. Most drugs related toxicities can be reversed on withdrawal or dose reduction of the offending drug. Liver eosionophila in the absence of organisms on special staining of biopsy specimen and compatible history highly suggests drug-induced liver disease. Alcoholic liver disease may co-exist with other lesions in patients with HIV infection. In previous studies 29% of AIDS patients had history of concomitant heavy alcohol use. 6% had alcoholic hepatitis and 7% had micronodular cirrhosis attributable to Alcohol [2, 5, 35,36,37].

Diagnostic approach

Opportunistic infections of liver are often secondary to infections in other parts of the body. Initial evaluation of these patients therefore requires a thorough history and physical examination. With special attention to prior opportunistic infections, use of potentially hepatotoxic drugs, alcohol use and travel which may reveal extrahepatic clues to the diagnosis. Clinicians must remember that HIV infected patients could get non-opportunistic non-HIV related diseases typical of their age and gender as well.

Laboratory work up should include absolute CD4 counts because its level could guide in possible types of infections and neoplasms. For instance mycobacterium tuberculosis infections and KS occur much earlier in immunosuppression compared with mycobacterium avium complex. Serological tests include alpha-fetoprotein, caeruloplamin, serum iron and total iron binding capacity, anti

nuclear factor, anti mitochondria and anti smooth muscle antibodies and alpha, anti trypsin to exclude non-AIDS related diseases. Liver associated enzymes will help separate hepaticellular from cholestatic abnormalities although the majority of the patients present with a mixed picture

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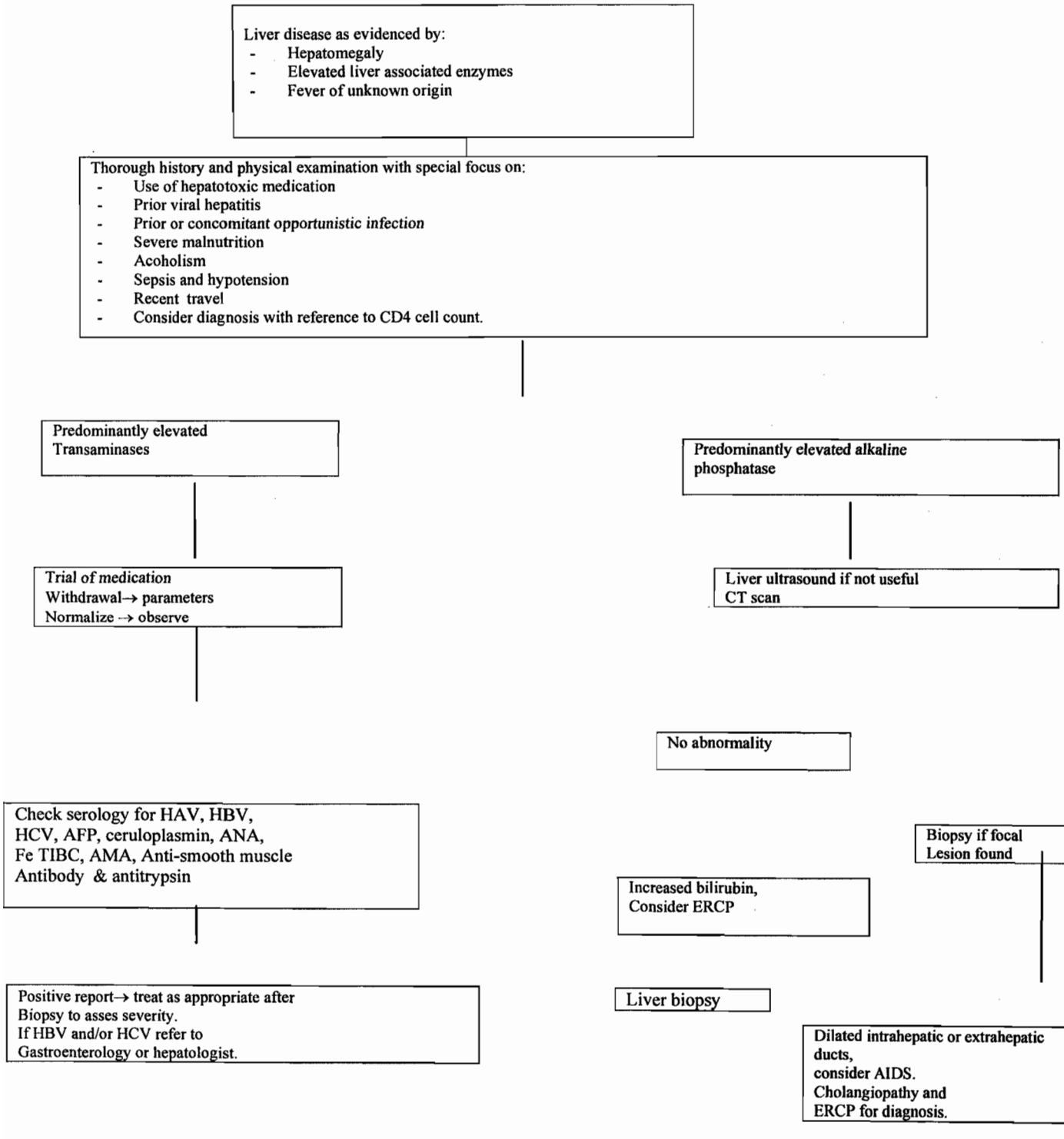
To assist in patient work up, an algorithm we found useful is presented below



Appendix 1.

Aetiology of liver disease in patients with advanced HIV infection.

Infections					Others
Viral	Bacterial	Protozoal	Fungal	Parasitic	**1.Mass lesions & neopla**
Hepatitis B, C, and D Cytomegalovirus (CMV) Epstein –Barr virus (EBV) Herpes simplex viruses (HSV) Adenoviruses Varicella zoster virus (VZV), HIV	Mycobacterial -Mycobacterium tuberculosis, Mycobacterium avium complex (MAC) Other atypical mycobacteria	Entamoeba histolytica Pneumocystis carinii Toxoplasma gondii Crytosporidium parvum Microsporidia	Histoplasma capsulatum Cryptococcus neoformans Coccidiodes immitis Candida albicans, and sometimes candida glabrata, candida tropicalis and candida krusei especially when response to azole antifungal agents is poor	Shistosoma species Stronglyoides species Leishamania donovani	-Kaposi's sarcoma Non-hodgkins lymphoma Peliosis hepatis **2. Toxins & drugs** Anti TB drugs, sulfonami cotrimoxazole, anti-convulsants, antieme ethanol.

Appendix ii

Table of potentially hepatotoxic drugs often required by patients with AIDS

Predominantly Hepatotoxic	**Predominantly cholestatic**	**Mixed**
Anti TB drugs; anti-fungal-azoles and amphotericin B; anti retroviral medication- zidovudine (AZT), dideoxyinosine(DDI) and all protease inhibitors (subclinical hepatitis); antibiotics- penicillins, metronidazole and tetracycline; antiviral agents – ganciclovir; anticonvulsantas – phenytoin and valproic acid.	Anti-emetics – phenothiazines, metoclopramide, chlorpromazine and prochlorperazine; antibiotics – azithromycin and erythromycin.	Chemotherapeutic agents-sulphonamides and cotrimoxale; pentamidine; carbamazepine; dapsone.