Management of Asymptomatic HIV Infection

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Contents

Summary

Patients are asymptomatic during the majority of HIV infection. The virus, however, is actively replicating, producing over 1 billion particles per day during this steady-state of the disease. Management of asymptomatic HIV infection involves initial recognition of infection and counselling to prevent its further spread.

When HIV infection has been confirmed, assessment consists of a careful history, physical examination and laboratory studies. The latter include serological tests for past exposure to infectious agents such as syphilis, hepatitis viruses, cytomegalovirus and toxoplasmosis. A purified protein derivative (PPD) skin test should also be performed. The immunological and virological status of the patient is assessed by quantifying CD4+ count and plasma HIV RNA levels. With the aid of these data, a decision can be made on the use of antiretroviral therapy.

Didanosine (ddI) is the only currently acceptable monotherapy. Combinations of antiretroviral drugs which have undergone evaluation include zidovudine (AZT) plus didanosine, zidovudine plus zalcitabine (ddC), zidovudine plus lamivudine (3TC), didanosine plus lamivudine, zidovudine plus didanosine plus nevirapine, zidovudine plus saquinavir, zidovudine plus zalcitabine plus saquinavir

(D4T), zidovudine plus ritonavir, zidovudine plus lamivudine plus indinavir, and ritonavir plus saquinavir.

The optimum combination treatment has not been defined, but many appear promising. In addition, treatment for subclinical infections and prophylaxis should be administered. These include treatment of all PPD-positive patients with isoniazid 300 mg/day orally for 1 year; prophylaxis against *Pneumocystis carinii* pneumonia for all patients with CD4+ counts <200/mm^3 with cotrimoxazole (trimethoprim plus sulfamethoxazole) one double-strength tablet daily, dapsone or dapsone plus trimethoprim; prophylaxis against toxoplasmosis in patients with CD4+ counts <100/mm^3 with cotrimoxazole or with dapsone plus pyrimethamine; prophylaxis against disseminated *Mycobacterium avium* complex disease in patients with CD4+ counts <75/mm^3 with azithromycin 1200mg orally once weekly, clarithromycin 500mg orally twice daily, or rifabutin 300 mg/day orally; and prophylaxis against *Streptococcus pneumoniae* pneumonia and bacteraemia by administration of the 23-valent pneumococcal vaccine.

Although cytomegalovirus disease occurs in most patients with advanced HIV disease (CD4+ <50/mm^3), primary prophylaxis is not recommended because of conflicting data concerning the efficacy of oral ganciclovir. Primary prophylaxis against cryptococcosis is not recommended because of the low incidence of this infection.

More than 15 years have elapsed since the first cases of AIDS were described in Los Angeles and New York. HIV, the cause of AIDS, was discovered in laboratories in France and the US in 1983. By 1996 it was estimated that 24 million individuals had already been infected by HIV throughout the world, 20 million infected individuals were living, and 10 000 new infections were occurring each day.[1] The vast majority of these individuals, if untreated, will experience inexorable virological, immunological and clinical deterioration culminating in an opportunistic infection, malignancy, wasting syndrome, dementia and death.

Patients can experience transient symptoms soon after acquisition of primary HIV infection. They generally develop symptoms during advanced diseases when they develop minor or major opportunistic infections, malignancy, wasting syndrome, encephalopathy or myelopathy. They are, however, asymptomatic for the majority of the time that HIV infection is present. It was thought that HIV was latent during most of this asymptomatic period. It is now recognised, however, that the virus is actively replicating, producing over a billion particles per day and destroying CD4+ cells at a prodigious rate during this steady-state of the disease.[2,3]

1. Assessment of Asymptomatic Patients

Management of patients during the asymptomatic period involves:
- recognition of the infection
- counselling to prevent its further spread
- diagnosis and treatment of coexistent disease
- assessment of the virological and immunological stage of HIV infection
- initiation of appropriate antiretroviral drugs
- initiation of appropriate prophylaxis to prevent infections.

For the most part, HIV testing in industrialised countries, such as the US, is voluntary. However, involuntary testing takes place on all blood donated for transfusion, in the military, in some prisons, among immigrants applying for permanent residence status and for insurance purposes. In federal Veterans Affairs medical facilities and in most states, written informed consent is required before voluntary HIV testing can be performed. Testing is advised for individuals who engage in high risk activities such as unprotected homosexual or pro-

miscuous heterosexual contact, and intravenous drug use. It is also recommended for patients with other sexually transmitted diseases and for all pregnant women.

HIV counselling is done in association with testing (table I). Counselling is done both before and after the test results are known. This 2-stage counselling is thought to be useful to give, and to reinforce, information about the limitations of the test, the nature of HIV infection and its relation to AIDS, the routes by which HIV infection is spread and the means to prevent this.

Once HIV infection is detected, the patient must be assured that they will have appropriate follow-up and treatment. Initial evaluation includes a thorough history and physical examination, with emphasis on symptoms and signs suggestive of the infections and malignancies that occur with increased frequency in HIV-infected patients. In addition, the clinician evaluates the patient's prior exposure to infectious diseases [by serological tests for syphilis, hepatitis B virus, hepatitis C virus, cytomegalovirus (CMV) and toxoplasmosis, and by a tuberculin skin test] and initiates appropriate treatment. Finally, the immunological status and HIV viral load of the patients are determined.

The immunological status of an HIV-infected patient is assessed by means of the CD4+ count, whose significance has been validated in several studies. For example, Fahey et al.[4] reported that the CD4+ count was the best of several cellular and serological predictors of clinical progression in the Multicenter AIDS Cohort Study (MACS), a large cohort of homosexual individuals who were recruited in 4 US cities between 1984 and 1985 and followed since. In addition, CD4+ count is inversely related to the risk of several opportunistic infections, including *Pneumocystis carinii* pneumonia (PCP), toxoplasmosis, cryptococcosis, disseminated *Mycobacterium avium* complex (DMAC) and CMV infection.[5] Monitoring for and prophylaxis against these are initiated as the CD4+ count falls.

Plasma HIV RNA levels provide important prognostic information. Three assay systems have been

Table I. Assessment of asymptomatic patients

Counsel and test for HIV antibody
Careful history and physical examination
Serological tests for syphilis, hepatitis viruses, cytomegalovirus and toxoplamosis
Skin test (PPD) for tuberculosis
CD4+ count
Quantify plasma HIV RNA
Abbreviation: PPD = purified protein derivative.

developed to quantify plasma HIV RNA. These are a branched DNA (bDNA) assay (Chiron), a reverse transcriptase polymerase chain reaction assay (Roche), and a nucleic acid sequence-based amplification assay (Organon Teknika). A recent review describes, compares, and makes recommendations for appropriate use of these tests to quantify HIV RNA.[6] Plasma HIV RNA levels are generally measured 3 to 4 times per year in association with the CD4+ count. They may also be quantified 4 to 6 weeks after initiation of a new or altered antiretroviral regimen to assess the response to therapy (see below).

In 1995, Mellors et al.,[7] using a bDNA assay, showed that the levels of HIV RNA in plasma obtained soon after a known date of seroconversion predicted the outcome of 62 patients. More recently, this group extended the studies of plasma HIV RNA levels to a large number of the MACS patients.[8] They demonstrated a direct relationship between the levels in plasma of HIV RNA in these patients and their risk for progression to AIDS or death. Further, they found that plasma HIV RNA levels were independent of CD4+ counts and were better predictors of progression than the latter.

Similar findings were reported from a multicentre haemophilia cohort study where a reverse transcriptase polymerase chain reaction assay system was used to quantify HIV RNA. In this study, O'Brien et al.[9] found that the risk of progression to AIDS among the patients with HIV-infected haemophilia was related to HIV RNA and to age but was not related to CD4+ count.

HIV RNA measurements were also assessed in retrospective studies of patients enrolled in AIDS

Clinical Trials Group (ACTG) protocol 116A, a randomised trial of zidovudine (AZT) compared with didanosine (ddI) in patients with little or no prior zidovudine experience.[10] HIV RNA was measured by both bDNA and reverse transcriptase polymerase chain reaction in this study, and the results obtained by these 2 methods were strongly correlated. Baseline HIV RNA and CD4+ counts proved to be independent predictors of disease progression in this study.

Changes in plasma HIV RNA levels and CD4+ counts predict clinical outcomes during treatment with antiretroviral drugs. This was demonstrated in a retrospective analysis of the Department of Veterans Affairs (VA) Cooperative Studies Program trial that compared early with delayed zidovudine treatment.[11] More recently, the value of HIV RNA levels for predicting prognosis and treatment effect was confirmed in ACTG protocol 175, a trial comparing monotherapy versus combinations of antiretroviral drugs.[12] In this latter study, both the baseline and treatment-associated changes in levels of plasma HIV RNA were independent predictors of clinical progression to AIDS or death, whereas CD4+ counts were not.

2. Antiretroviral Treatment

A number of antiretroviral drugs have been approved by the US Food and Drug Administration (FDA) and are listed in table II. An international panel of experts recommended that antiretroviral treatment should be started for all symptomatic HIV-infected patients and most asymptomatic patients with CD4+ counts of $<500/mm^3$.[13] However, they acknowledged a paucity of prospective data concerning the management of patients with stable CD4+ counts of 350 to $500/mm^3$ with low or undetectable plasma HIV RNA levels. Further, the only randomised, placebo-controlled trial conducted to date in asymptomatic patients with initial CD4+ counts of $>500/mm^3$ showed no benefit to early treatment.[14]

Despite these limitations, the 3 basic principles of antiretroviral treatment for asymptomatic HIV-infected patients are:

- Treatment should be considered for all patients with HIV infection. It should be strongly recommended for those with HIV RNA levels of $>10\,000$ copies/mm^3, with rising levels of HIV RNA or with falling CD4+ count.
- For those with low or undetectable plasma levels of HIV RNA and stable CD4+ counts, careful monitoring at 3- to 4-month intervals without antiretroviral treatment should be considered.
- Response to antiretroviral treatment should be monitored by quantifying plasma HIV RNA for 4 to 6 weeks after initiation of treatment.

2.1 Monotherapy with Antiretroviral Drugs

Monotherapy with antiretroviral drugs at best provides transient clinical benefit for asymptomatic patients. Zidovudine is the oldest and best evaluated of the antiretroviral drugs. The effects of zidovudine monotherapy have been studied in asymptomatic patients at varying stages of disease. For example, more than 1600 patients with initial CD4+ counts of $>500/mm^3$ were entered into a randomised ACTG trial comparing 500 mg/day, 1500 mg/day or delayed zidovudine therapy.[14] After a mean of 4.8 years of follow-up, there were no significant differences in the AIDS-free or overall survival of the treatment groups.

Table II. Antiretroviral drugs

Drug	Generic name	Oral dose (mg)	Estimated daily cost, 1996 ($US)
Nucleoside analogues			
AZT	Zidovudine	200 tid	9.30
ddI	Didanosine	200 bid	6.00
ddC	Zalcitabine	0.75 q8h	6.90
d4T	Stavudine	40 bid	8.10
3TC	Lamivudine	150 bid	7.40
Protease inhibitors			
SQV	Saquinavir	600 tid	19.00
RTV	Ritonavir	600 bid	22.00
IND	Indinavir	800 tid	15.00
Non-nucleoside reverse transcriptase inhibitor			
NVP	Nevirapine	200 bid	5.22

Abbreviations: bid = twice daily; q8h = every 8 hours; tid = 3 times daily.

Zidovudine monotherapy has also been evaluated in patients with more advanced HIV infection. VA, ACTG protocol 019 and Concorde studies provide examples of the transient benefits of zidovudine monotherapy.[15-18] In the VA Cooperative Studies trial, early versus delayed zidovudine treatment reduced the risk of progression to AIDS but did not improve survival.[15] In the ACTG protocol 019 study, zidovudine compared with placebo treatment provided initial protection against clinical progression but no survival benefit.[16] However, the protection against clinical progression in this study diminished after 2 years of follow-up.[17] In Concorde, neither progression to AIDS nor survival was improved in the patients who received early compared with deferred zidovudine treatment.[18]

Monotherapy with didanosine has also been extensively studied. ACTG protocol 116A was a randomised trial of zidovudine compared with high or low dose didanosine monotherapy for patients who had received little or no prior zidovudine therapy.[19] It showed a reduced rate of clinical progression among the patients randomised to zidovudine with no prior zidovudine therapy. It also showed a reduced rate of clinical progression among the patients randomised to didanosine who had received as little as 8 to 16 weeks of prior zidovudine therapy.

Three other studies confirmed these latter results. In ACTG protocol 116B/117, patients who had received at least 16 weeks of zidovudine treatment were randomly assigned to continue on zidovudine or to receive high or low dose didanosine.[20] The patients assigned to low dose didanosine had significantly reduced risk of progression compared with those remaining on zidovudine.

The Canadian Network conducted a randomised trial comparing zidovudine with didanosine in patients with 6 months of prior zidovudine experience and CD4+ counts of 200 to 500/mm^3.[21] There were significantly fewer AIDS events in the group assigned to didanosine.

Finally, a multicentre, randomised, double-blind study compared continued zidovudine with didano-sine therapy in patients who received zidovudine for at least 6 months and had signs of clinical deterioration.[22] There was a reduced risk of clinical progression to a new AIDS event or death among the group assigned to didanosine. These studies confirm a time-limited benefit to zidovudine monotherapy as well as a benefit to a switch to didanosine.

Experience with other nucleoside analogues as monotherapy for HIV infection is more limited. For example, Fischl et al.[23] reported results of a randomised trial comparing continued zidovudine with zalcitabine (ddC) in patients who had experienced a first episode of PCP or advanced AIDS and had tolerated a minimum of 48 weeks of zidovudine treatment. No differences were observed in survival or clinical end-points. The Community Program for Clinical Research on AIDS (CPCRA) conducted a randomised trial comparing didanosine with zalcitabine in patients who progressed on or were intolerant of zidovudine treatment.[24] Progression or death occurred in 93.3 and 87.8% of the patients randomised to didanosine and zalcitabine, respectively (p = 0.15).

Fischl et al.[25] reported the results of a randomised trial comparing continued zidovudine, zalcitabine or the combination of zidovudine plus zalcitabine in patients who had tolerated at least 6 months of zidovudine treatment. Patients were stratified on the basis of their prerandomisation CD4+ counts. There were no overall outcome differences between the treatment groups. However, in the subset of patients with the highest pretreatment CD4+ count, there were fewer progressions or deaths in those randomised to the combination of zidovudine plus zalcitabine compared with zidovudine treatment. These data support the use of a combination of antiretroviral drugs, more fully discussed in section 2.2.

2.2 Combination Therapy with Antiretroviral Drugs

Combinations of antiretroviral drugs to treat HIV infection are advocated for several reasons.

- HIV replicates in patients at an enormous rate. As noted above, infected patients produce more than 1 billion (10^9) HIV virions daily during the steady-state of infection.
- Most of the nucleoside analogues have relatively modest antiretroviral activity when used alone, reducing viral loads by <1 log even during early stages of treatment.[11,12,26]
- Monotherapy results in the selection of resistant HIV strains and uninhibited replication of these is associated with clinical deterioration.[27-29]
- The clinical benefits of early monotherapy with antiretroviral drugs, such as zidovudine, have proven to be transient.[15-18]

2.2.1 Nucleoside Analogues

A number of antiretroviral drug combinations have been evaluated in HIV-infected patients. ACTG protocol 175[30] and the European/Australian Delta Trials[31] compared the risks of clinical disease (progression to AIDS or death) in patients randomised to receive the combinations of zidovudine plus didanosine or zidovudine plus zalcitabine with zidovudine monotherapy. The patients enrolled in ACTG 175 had CD4+ counts between 200 and 500 cells/mm³, while those in the Delta Trial had CD4+ counts of <350/mm³.

In both studies, patients randomised to the zidovudine plus didanosine combination were significantly less likely to progress than those randomised to zidovudine monotherapy. In ACTG 175, this benefit was observed among all of the subsets, whereas in the Delta Trial, involving more advanced patients, the benefit was observed only among those patients who were initially zidovudine-naive. The patients randomised to zidovudine plus zalcitabine also received a marginal benefit. In ACTG 175, one group of patients was randomised to didanosine monotherapy; this group did as well as those randomised to zidovudine plus didanosine.

A CPCRA trial also compared the combinations of zidovudine plus didanosine, zidovudine plus zalcitabine and zidovudine monotherapy.[32] In this study, patients with AIDS or with CD4+ counts of <200/mm³ were randomised to the 3 treatment arms. Although the overall AIDS-free survival and

survival were essentially the same in the treatment arms, the patients who had not received prior zidovudine treatment and were randomised to the combination treatments appeared to benefit.

The data from these 3 trials suggest that a combination of two new (previously unused) antiretrovirals may be required for clinical benefit in patients with advanced HIV infection, whereas didanosine monotherapy may be acceptable in less advanced patients.

Lamivudine (3TC) is a potent reverse transcriptase inhibitor which has a broad range of activity against HIV. Mutations at codon 184 of the polymerase gene occur rapidly in patients exposed to this agent and confer resistance to it.[33] These strains, however, remain sensitive to zidovudine.[34] A double-blind study was conducted in HIV-infected patients with CD4+ counts of 200 to 500 cells/mm³ already on treatment with zidovudine.[35] The patients were randomly assigned to receive treatment with zidovudine alone, lamivudine alone or a combination of zidovudine plus lamivudine. The combination was well tolerated by the study participants. Further, the patients on combined treatment had a striking increase in their CD4+ counts and reduction in their plasma HIV RNA levels which persisted over both the initial period and an extended period of 52 weeks of blinded follow-up.[36]

Another study compared the combinations of zidovudine plus lamivudine [given in low (150mg twice daily) or high (300mg orally twice daily) doses] with zidovudine plus zalcitabine in patients already on zidovudine with CD4+ counts of 100 to 300 cells/mm³.[37] The patients randomised to the zidovudine plus lamivudine combinations had an increase in their CD4+ counts, but HIV RNA levels were similar for all groups. Further, the low doses of lamivudine were better tolerated. However, there were too few end-points to draw any conclusions about the clinical benefits of the combination of zidovudine plus lamivudine in either of these studies.

2.2.2 Non-Nucleoside Reverse Transcriptase Inhibitors

Nevirapine is the first non-nucleoside reverse transcriptase inhibitor to receive conditional approval for use by the FDA. A pilot study in asymptomatic patients showed that nevirapine monotherapy resulted in rapid selection of resistant strains.[38] A study comparing the combination of nevirapine plus zidovudine plus didanosine with the combination of zidovudine plus didanosine was recently reported.[39] After 48 weeks of treatment, patients assigned to the triple combination had a higher mean CD4+ count and a lower mean HIV RNA concentration than did those assigned to the double combination. However, the patients assigned to receive nevirapine also experienced more severe rashes, and there were no differences in the risks for disease progression in the small groups of patients studied. On the basis of these findings, enthusiasm for this combination must be very limited.

2.2.3 Protease Inhibitors

Saquinavir was the first of the protease inhibitors to receive conditional approval for use by the FDA. It was evaluated by the AIDS Clinical Trials Group (ACTG) in Protocol 229. In this study, patients with prior zidovudine experience were randomly assigned to receive zidovudine plus zalcitabine, zidovudine plus saquinavir, or the triple combination of zidovudine, zalcitabine and saquinavir.[40] After 48 weeks of therapy, 51% of the patients on triple therapy, 34% on zidovudine plus zalcitabine and 33% on zidovudine plus saquinavir had CD4+ counts above baseline (p = 0.0013). On triple therapy, HIV RNA titres initially fell by 0.8 log, while they fell 0.4 logs on the double therapy combinations (p < 0.001). Again, clinical evidence of efficacy is lacking.

Ritonavir is a potent HIV protease inhibitor which has high oral bioavailability. Preliminary clinical results of a multicentre, double-blind trial of ritonavir were recently reported.[41] HIV infected patients with CD4+ counts of 100 cells/mm^3 were randomly assigned to receive ritonavir in a dose of 600mg orally twice daily or placebo. Other anti-

retroviral drugs were permitted. The end-points of the study were AIDS-defining events and death. Adverse events were observed in 17% of the patients receiving ritonavir and 6% of the placebo recipients. These included nausea, vomiting, weakness and diarrhoea. In a median of 6.1 months of follow-up, there were 26 (4.8%) deaths in 543 patients assigned to ritonavir compared with 46 (8.4%) deaths in 547 patients assigned to placebo (p = 0.02). AIDS or death were observed in 69 (12.7%) and 149 (27.3%) of the patients assigned to ritonavir and placebo, respectively (p < 0.001). There was a surprisingly large number of Kaposi's sarcoma AIDS-defining diagnoses in the placebo group. However, these data suggest that ritonavir treatment is associated with a substantial benefit in preventing morbidity and mortality in patients with advanced HIV infection.

Indinavir is another potent HIV protease inhibitor with high oral bioavailability. Nephrolithiasis is a significant side effect of treatment with this drug. A double-blind trial of indinavir in patients with 6 months of zidovudine treatment, CD4+ counts of 50 to 400 cells/mm^3 and plasma HIV RNA levels of >20 000 copies/ml was recently reported.[42] A total of 97 patients were randomly assigned to receive indinavir alone, zidovudine plus lamivudine or indinavir plus zidovudine plus lamivudine. Plasma HIV RNA levels fell to below the lower limit of detection (<500 copies/ml) in 88 and 84% of the patients on triple therapy and 41 and 44% of the patients on indinavir alone at 12 and 24 weeks of treatment, respectively. In contrast, undetectable levels of plasma HIV RNA were observed in only 8% of the patients on zidovudine and lamivudine at 12 weeks and none at 24 weeks of therapy.

These data suggest that the combination of indinavir plus zidovudine plus lamivudine is the most potent combination of antiretroviral drugs tested to date. A trial of indinavir with clinical end-points is now in progress.

Finally, preliminary results have been reported of a trial in which patients received a combination of 2 protease inhibitors, saquinavir plus ritonavir.[43]

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Table III. Treatment and prophylaxis for infections in patients with asymptomatic HIV infection

Infection	Indication	Preferred therapy/prophylaxis	Alternative
Tuberculosis	Positive PPD	INH 300 mg orally daily	Rifampicin (rifampin); pyrazinamide + ethambutol; pyrazinamide + fluoroquinalone
PCP	CD4+ ≤200	Daily TMP-SMX DS	Dapsone; dapsone + trimethoprim; aerosol pentamidine
Toxoplasmosis	CD4+ <100	Daily TMP-SMX DS	Dapsone + pyrimethamine
DMAC	CD4+ <75	Azithromycin 1200 mg/wk	Clarithromycin 500mg bid; rifabutin 300mg od
CMV	CD4+ <50	None	Oral ganciclovir 1g PO tid
Cryptococcosis	CD4+ <50	None	Fluconazole 200 mg/day PO
S. pneumoniae	All HIV+	Pneumococcal vaccine	

Abbreviations: bid = twice daily; CMV = cytomegalovirus; DMAC = disseminated *Mycobacterium avium* complex; od = once daily; INH = isoniazid; PCP = *Pneumocystis carinii* pneumonia; PPD = purified protein derivative; PZA = pyrazinamide; PO = orally; tid = 3 times daily; TMP-SMX DS = cotrimoxazole (trimethoprim plus sulfamethoxazole), double strength; TMP = trimethoprim.

In this study, patients with CD4+ counts of 100 to 500/mm^3 were randomly assigned to 1 of 4 regimens combining these drugs. Median plasma HIV RNA levels fell 2 to 3 logs from baseline levels with each of the regimens tested, and they were generally well tolerated. Long term follow-up and clinical studies of protease inhibitor combinations are pending.

The above data suggest that combinations of antiretroviral drugs are appropriate for most patients receiving treatment. didanosine is the only antiretroviral agent which can be used alone, and this should be selected only in patients with less advanced disease, such as those with CD4+ counts of 350 to 500/mm^3 and a plasma HIV viral load of <10 000. Although optimal regimens for patients with more advanced disease have not been established by comparative clinical trials, combinations including a protease inhibitor with one or more new nucleoside analogues or a combination of protease inhibitors seem most promising.

3. Additional Treatment and Prophylaxis

Infections caused by other micro-organisms produce much of the morbidity and mortality in HIV-infected patients. Clinically active infections are generally associated with symptoms. Their treatment, therefore, is beyond the scope of this article. Many organisms, however, cause latent infections which can be detected and treated before symptoms occur. Others can be prevented by appropriate immunisations or use of antimicrobial

agents. Some of these are shown in table III and discussed below.

3.1 Tuberculosis

Clinically active *Mycobacterium tuberculosis* infection occurs at all stages of HIV disease. The tuberculin skin test is the most sensitive means of detecting asymptomatic, subclinical *M. tuberculosis* infection. Induration of 5mm is considered to be positive in HIV-infected patients, and 8% per year of the PPD-positive, HIV-infected patients develop clinically active disease.[44] A case-control study showed that clinical tuberculosis also accelerates the downhill course of HIV infection.[45]

A year of preventive treatment with isoniazid 300mg orally daily plus pyridoxine 50mg orally daily is recommended for tuberculin-positive HIV-infected patients with no evidence of clinical disease.[46] For those known to have been exposed to patients with multi–drug-resistant *M. tuberculosis* infections, reasonable alternatives are treatment with rifampicin (rifampin) 600mg orally daily, pyrazinamide plus ethambutol or pyrazinamide plus a fluroquinolone.

3.2 *Pneumocystis carinii* Pneumonia

PCP is the most common life-threatening opportunistic infection that occurs in HIV-infected patients. Most PCP infections occur in patients with CD4+ counts of 200/mm^3.[47] Such patients should be given prophylaxis. Randomised, controlled clinical trials showed that cotrimoxazole is the most

effective agent for prophylaxis against both primary[48] and recurrent[49] PCP infection and will prevent most disease if used properly. However, allergy to or intolerance of cotrimoxazole is common among HIV-infected patients. Therefore, alternatives may be required, such as dapsone, dapsone plus trimethoprim, or aerosolised pentamidine.[50]

3.3 Toxoplasma Encephalitis

Toxoplasma gondii is an obligate intracellular parasite which causes encephalitis and disseminated disease in HIV-infected patients. Most infections occur as a result of reactivation of latent infection in *T. gondii* seropositive, HIV-infected patients with CD4+ counts of $100/mm^3$.[51] Such patients should be considered for prophylaxis, even when asymptomatic. Fortunately, cotrimoxazole, one of the agents used to prevent PCP infection, appears to be effective against *T. gondii* also.[52] The combination of dapsone and pyrimethamine is an alternative in those who are allergic to or cannot tolerate cotrimoxazole.

3.4 Disseminated *Mycobacterium avium* Complex Disease

DMAC is the most common opportunistic bacterial infection occurring in patients with HIV infection. For example, Nightingale et al. followed over 1000 patients after a clinical diagnosis of AIDS and demonstrated, by monthly lysis-centrifugation of blood cultures, that the incidences of MAC bacteraemia were $21 \pm 2\%$ and $41 \pm 3\%$ at 1 and 2 years, respectively.[53] Most DMAC infections occur at late stages of HIV infection. In the study cited above, the 1-year incidence of MAC bacteraemia was 39, 30, 20, 15, 8, 3 and 1% for patients with CD4+ counts of 0 to 9, 10 to 19, 20 to 49, 40 to 59, 60 to 99, 100 to 199 and 200 to 499 cells/mm^3, respectively. The median survival of patients following diagnosis of MAC bacteraemia was 134 days.

Three drugs have been shown to be effective as prophylaxis against DMAC infections in randomised, controlled clinical trials. These are rifabutin,[54] clarithromycin[55] and azithromycin.[56] Un-

fortunately, breakthrough infections occur with these agents. The DMAC isolates obtained from patients receiving rifabutin prophylaxis are generally sensitive to rifabutin, whereas those isolated from patients on either clarithromycin or azithromycin prophylaxis are generally resistant to both clarithromycin and azithromycin. At present, DMAC prophylaxis is recommended for patients with CD4+ counts of $<75/mm^3$.[57] However, the agents used for prophylaxis may interact with antiretroviral drugs such as protease inhibitors. Since it is not yet known whether the virological and immunological improvement which occurs on treatment will reduce the risk of DMAC infections, many experts defer DMAC prophylaxis until combinations of antiretroviral drugs fail or are not tolerated.

3.5 Cytomegalovirus Disease

CMV disease is demonstrated clinically or by autopsy in most patients with HIV infection. The most common manifestation of CMV in HIV-infected patients is retinitis which can lead to blindness. CMV also causes ulcerative gastrointestinal disease, encephalitis, polyradiculitis, pneumonia and adrenalitis.

One randomised, placebo-controlled trial in HIV-infected patients showed that oral ganciclovir significantly reduced the incidence of CMV disease but did not improve overall survival.[58] However, a second trial, conducted by the CPCRA, showed no differences in the incidence of CMV disease in the placebo and ganciclovir recipients.[59] There were significantly more adverse events in the patients randomised to ganciclovir than in the placebo recipients.

Analysis suggested that in 1996 it cost $US144 000 to prevent each case of CMV disease and $US15 000 to extend disease-free survival by 1 month.[60] On the basis of these data, most experts do not recommend the use of oral ganciclovir for primary CMV prophylaxis at this time.

3.6 Invasive Fungal Infections

Cryptococcus neoformans and *Candida* spp. cause invasive disease in patients with advanced HIV in-

fection. *Candida* oesophagitis generally follows a more localised oral infection which is likely to produce symptoms. Cryptococcosis, in contrast, frequently occurs in previously asymptomatic patients. A randomised trial compared the efficacy of oral fluconazole with clotrimazole troches as prophylaxis against invasive fungal infection.[61] Patients randomised to the latter had significantly increased risk of cryptococcosis (relative hazard 8.5; 95% CI 1.9 to 37.6). Most of the cryptococcal infections occurred in patients with baseline CD4+ counts of <50/mm^3, and 78% of them in patients whose most recent CD4+ count was below this level. Despite these data, prophylaxis to prevent cryptococcosis is not recommended because of the relatively low incidence of this infection and the expense of prophylactic treatment. In the randomised trial described above, it was estimated that 11 756 doses of fluconazole were administered at a cost of over $US100 000 for each case of cryptococcosis prevented.

3.7 *Streptococcus pneumoniae* Infections

S. pneumoniae is the most common cause of community-acquired bacterial pneumonia in HIV-infected patients.[62] Though they are not associated with increased mortality, bacteraemic pneumococcal infections occur far more commonly in HIV-infected than in non–HIV-infected patients.[63] Many of these infections can be prevented by use of the 23-valent pneumococcal capsular polysaccharide vaccine. Pneumococcal vaccine failures have been reported in HIV-infected patients.[64] However, asymptomatic individuals with relatively intact immune systems appear to respond normally to the pneumococcal vaccine.[65] The Advisory Committee on Immunisation Practices to the US Public Health System recommends the use of pneumococcal vaccine for all HIV-infected patients.[66]

4. Conclusions

Patients are asymptomatic during most of the initial phases of HIV infection. The virus, however, is actively replicating during this period. Manage-ment of asymptomatic HIV infection involves recognition of infection and counselling to prevent its further spread. When HIV infection has been confirmed, assessment consists of a careful history, physical examination and laboratory studies. The latter includes serological tests for past exposure to infectious agents such as syphilis, hepatitis viruses, cytomegalovirus and toxoplasmosis. A PPD skin test also should be performed.

Immunological and virological status of the patient are assessed by quantifying CD4+ count and plasma HIV RNA concentrations. With the aid of these data, a decision on use of antiretroviral therapy can be made. Didanosine is the only currently acceptable monotherapy. Combinations of antiretroviral drugs which have undergone evaluation include zidovudine plus didanosine, zidovudine plus zalcitabine, zidovudine plus lamivudine, didanosine plus lamivudine, zidovudine plus didanosine plus nevirapine, zidovudine plus saquinavir, zidovudine plus zalcitabine plus saquinavir, zidovudine plus ritonavir, zidovudine plus lamivudine plus indinavir, and ritonavir plus saquinavir. The optimum combination and timing of treatment have not been defined. Future research should clarify these.

In addition to antiretroviral therapy, treatment for subclinical infections and prophylaxis should be administered. These include:

- Treatment of all PPD positive patients with isoniazid 300 mg/day orally for 1 year.
- Prophylaxis against PCP for all patients with CD4+ counts <200/mm^3 with trimethoprim plus sulfamethoxazole one double-strength tablet daily, dapsone or dapsone plus trimethoprim.
- Prophylaxis against toxoplasmosis in patients with CD4+ counts <100/mm^3 with trimethoprim plus sulfamethoxazole or with dapsone plus pyrimethamine.
- Prophylaxis against DMAC disease in patients with CD4+ counts <75/mm^3 with azithromycin 1200mg orally once weekly, clarithromycin 500mg orally twice daily, or rifabutin 300 mg/day orally.
- Prophylaxis against *S. pnuemoniae* pnuemonia and bacteraemia by administration of the 23-valent pneumococcal vaccine.

Future research also should define more effective means of preventing or suppressing the host of infections that complicate HIV disease.

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