The management of opportunistic infections in the era of highly active antiretroviral therapy

Elena Ferrer and Daniel Podzamczer

Service of Infectious Diseases, Ciutat Sanitària i Universitària de Bellvitge, L'Hospitalet, Barcelona, Spain

Abstract

Major improvements have occurred in HIV infection in recent years. Potent antiretroviral therapies have reduced dramatically the number of subjects with low CD4 counts and high viral burden. As result, most HIV-infected persons are no longer at risk to develop opportunistic infections and therefore primary prophylaxis is rarely recommended. Moreover, in patients who were receiving secondary prophylaxis after suffering a first episode of Pneumocystis carinii pneumonia, cytomegalovirus retinitis or toxoplasmosis of the central nervous system, recent evidences support the discontinuation of preventive medication as soon as the increase in CD4+ cell count produced by the newly potent antiretroviral drugs reach a certain threshold. Any reduction in the number of drugs prescribed in those patients is of great benefit in terms of quality of life and reduction in the risk of toxicities and drug interactions.

Key words

Oportunistic infections. Prophylaxis. HAART

Introduction

Opportunistic infections (OI) have been the leading cause of morbidity and mortality among patients with advanced HIV infection since the start of the AIDS epidemic[1-3]. At the same time, primary and secondary prophylaxis for some of the main OI have been one of the main therapeutic strategies used to reduce complications associated with the disease, and to prolong patient survival[4-11].

The use of highly active antiretroviral therapy (HAART) over the last 4-5 years has considerably affected the evolution of HIV infection[12-14]. Powerful therapies are able to suppress viral replication over substantial periods of time, and allow at least a partial reconstitution of the immune system[15-19]. This has led to a notable reduction in the incidence of OI and other AIDS complications (Kaposi's Sarcoma, HIV encephalitis, wasting syndrome), as well as contributing to a drastic reduction in mortality rates and hospital stays among HIV-positive patients in recent years (Fig. 1)[14,20-22].

Among the changes in OI that will be described in this chapter two of critical. First, the atypical clinical manifestations of diseases occurring in conjunction with the administration of HAART[23-27], and second, the recent proposals for the discontinuation of primary and secondary prophylaxis for certain OI in patients in whom immunity has been restored.

The incidence of OI in the HAART era

In countries where combined antiretroviral drug regimens, which include either protease inhibitors or non-nucleoside reverse-transcriptase inhibitors, are used, a reduction in the incidence of OI of between 50 and 80% has been observed, depending

Correspondence to:
Daniel Podzamczer
Service of Infectious Diseases
Ciutat Sanitaria i Universitaria de Bellvitge
Crta. de la Feixa Llarga s/n
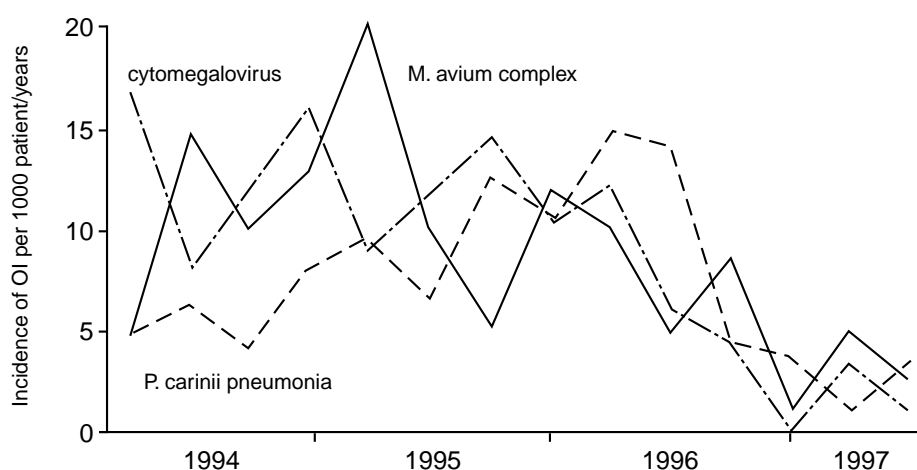08907 Hospitalet, Barcelona, Spain

Fig. 1. *Reduction in the incidence of the most frequent opportunistic infections (OI) in the HAART era. Adapted from Palella et al.[14].*
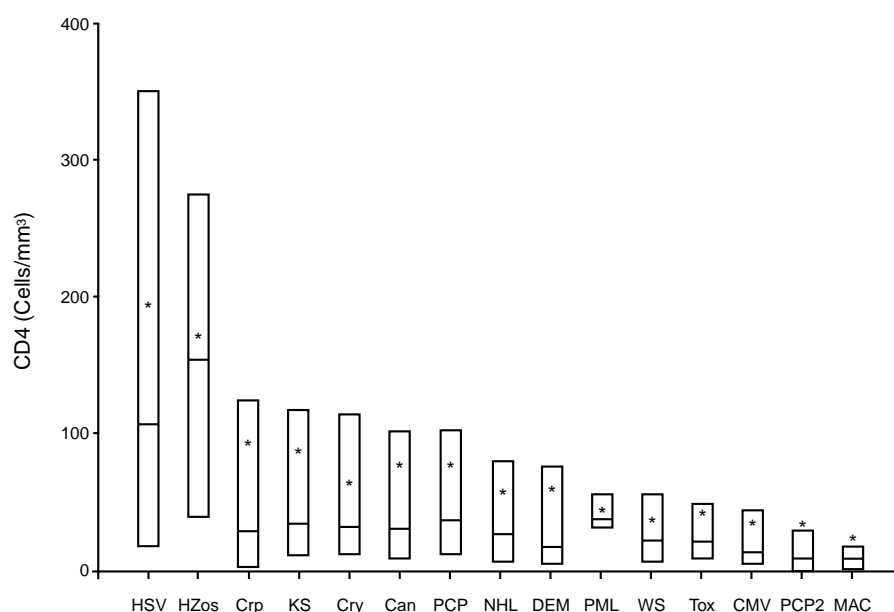

Fig. 2. *Relation between CD4 count and appearance of opportunistic infections (the lines dividing the bars represent median values; the asterisks represent the mean values). Adapted from Moore and Chaisson[43].*

on the area and the particular OI[12-14,28,29]. The greatest decrease has been seen in disseminated *Mycobacterium avium* complex or citomegalovirus infections and to a lesser extent in those caused by *P. carinii*. These variations may indicate that restoring immunity does not protect equally against all OI, although other factors, such as the different uses of prophylaxis or changes in diagnostic and therapeutic approaches, may play a role.

A large number of OI observed today appear in individuals who either have not yet been diagnosed with HIV, or do not accept antiretroviral treatment or whose drug has failed due to non-adherence to therapy, drug resistance or other factors[30-32]. A considerable percentage of these patients do not receive appropriate prophylaxis in first episodes of opportunistic infections.

Immunity and OI

Higher levels of immunodeficiency in the advanced HIV+ patient mean a higher probability of contracting an OI[33-35], with CD4 T-lymphocyte count being the best predictor of the appearance of OI.
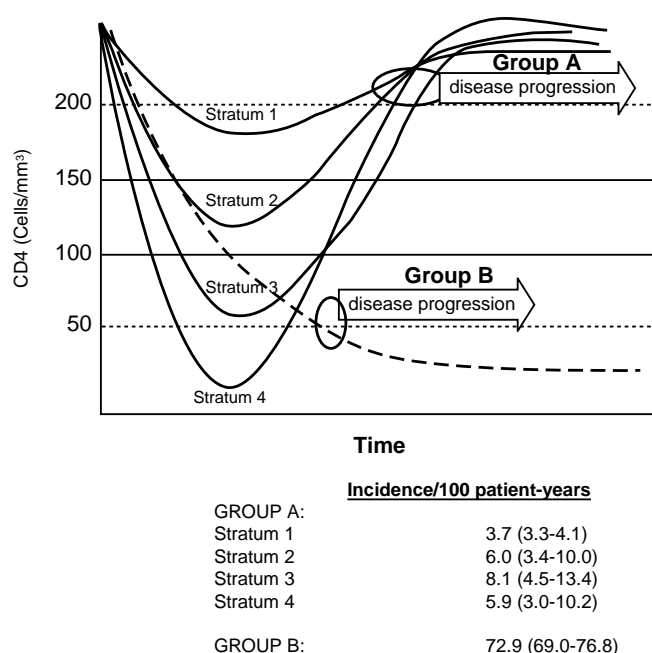
Fig. 3. *Incidence of opportunistic infections in relation to the nadir CD4 count. Group A: Patients who have recovered to CD4 > 200 cells/mm³. Group B: Patients with CD4 counts remaining < 50 cells/mm³. Adapted from Miller et al.[13].*

While the percentage of CD4 lymphocytes is the most stable indicator, the absolute CD4 cell count is more frequently used in decisions regarding the initiation of prophylactic therapy (and, more recently, in decisions regarding the discontinuation of such therapy)[35]. Although HIV viral load is an excellent indicator of the progression to AIDS [36,37], its relation to the appearance of OI has not been well established yet[38]. Several studies have suggested that viral load may be a good, independent indicator of the appearance of OI[39], but the CD4 count, rather than the viral load, is generally the best predictor, particular-

ly in the short term[40,41] and even when viral load is very high.

Not all OI occur at the same level of immunodeficiency. Thus, while tuberculosis and oesophageal candidiasis may appear when immunity is still relatively well preserved (CD4 > 200 cells/mm³), other OI, such as *P. carinii* pneumonia and toxoplasmosis, appear only when CD4 counts fall below 200 cells/mm³. The risk of toxoplasmosis increases only if the CD4 count is <100 cells/mm³. MAC or CMV infections only appear in patients who are severely immunosuppressed (CD4 < 50 cells/mm³) (Fig. 2)[42,43].

Table 1. *Recommendations for minimising exposure to selected pathogens among patients with HIV infection[6]*

Pathogen	Intervention
Pneumocystis carinii	Avoid sharing hospital room with patients who have active *P. carinii* pneumonia (may not be a valid recommendation).
Toxoplasma gondii	Avoid eating undercooked red meat and wash fruit and vegetables before eating them uncooked. Avoid contact with cat faeces.
Cryptosporidium	Avoid drinking unprocessed ground water; use only bottled or processed water; avoid household pets less than 6 months of age, particularly if they have had diarrhoea; always practice good hygiene in caring for children.
Mycobacterium tuberculosis	Avoid high-risk jobs such as assisting the homeless and certain health care situations.
Cytomegalovirus	If the patient is seronegative for CMV, avoid transfusions with seropositive patients, avoid unprotected sex. Always maintain good hygiene in caring for children.
Human Papillomavirus, Herpes simplex and Hepatitis B	Avoid unprotected sex.
Histoplasma capsulatum	In endemic areas: avoid high risk activities (cave exploring, cleaning chicken coops) and contact with faeces of wild birds.

Table 2. *Drug regimens for primary and secondary prophylaxis for the most common opportunistic infections*

Pathogen	Primary	Secondary
Pneumocystis carinii	**CD4 < 200 or < 14%, or oral candidiasis** Cotrimoxazole (160 mg trimethoprim + 800 mg sulfamethoxazole qd, 3 d/week). Dapsone 100 mg + pyrimethamine 50 mg 2 d/week. Aerosolised pentamidine 300 mg/month. Fansidar (500/25 mg), 1-2 days/week.	**Previous episode of PCP** Cotrimoxazole dosage identical to the primary prophylaxis. Aerosolised pentamidine, 300 mg/15 d. Pentamidine iv or im, 4 mg/kg/month. Dapsone, 100 mg/d or 200 mg/week. Fansidar (500/25 mg), 1-2/week.
Toxoplasma gondii	**CD4 < 100 and *T. gondii* seropositive** Cotrimoxazole (160/800 mg) qd, 3 d/week. Dapsone, 100 mg + Pyrimethamine 50 mg, 2 d/week. Pyrimethamine, 50 mg 3 d/week (+ folinic acid).	**Previous episode of toxoplasmosis** Sulfadiazine 2 g + pyrimethamine 25 mg + folinic acid 10 mg qd, daily; or sulfadiazine 2 gr + pyrimethamine 50 mg + folinic acid 10 mg qd 3 days per week Clindamycin, 600 mg tid + pyrimethamine, 25 mg + folinic acid, 10 mg qd. Clarithromycin 500 mg/12 h + pyrimethamine, 25 mg + folinic acid, 10 mg/d.
Leishmania donovani	No	**Previous episode of leishmaniasis** Glucantime 20 mg/Kg/15-30 days
Isospora belli	No	**Previous episode of isosporiasis** Cotrimoxazole (160 mg trimethoprim + 800 mg sulfamethoxazole), 3 days/week. Fansidar 1 tablet/week
Cryptococcus neoformans	**CD4 < 50 (selected cases)** Fluconazole 100-200 mg qd	**Previous episode of criptococosis** Fluconazole 200 mg qd. Amphotericin B 100 mg/week iv.
Candida sp.	No	**Severe recurrent candidiasis** Topical nistatin or miconazole. Fluconazole 50-100 mg qd Ketoconazole 200-400 mg qd Amphotericin B 0.2-0.3 mg/kg/d iv (esophageal or candida resistant to imidazoles).
Cytomegalovirus[a]	**CD4 < 50 and Ag pp65 or PCR-CMV + (selected cases)** Ganciclovir 1 g tid oral	**Previous episode of retinitis (other sites)** Ganciclovir 5 mg/kg/d iv 5 d/week or 10 mg/kg/d 3 d/week or ganciclovir orally 1 g tid. Foscarnet 120 mg/kg/d iv in 2-3 h, 5 d/week. Cidofovir 5 mg/kg iv + probenecid every 2 weeks.
Herpes simplex	No	**Frequent recurrence** Aciclovir 200 mg tid or 400 mg bid Famciclovir 500 mg bid Valaciclovir 500 mg bid
Herpes zoster	**Recent contact with VVZ and no prior incidents** VZIG 5 vials (of 1.25 mL) im 48-96 h after exposure.	**Frequent recurrence** Aciclovir 800 mg bid or tid, if recurrence is frequent. Famciclovir 500 mg bid
M. tuberculosis	**PPD+ (current or previous) without prophylaxis or prior treatment.** **Recent contact with BAAR+** Isoniazid 300 mg qd or 900 mg 2 d/week, for 9 months. Rifampin 600 mg + pyrazinamide 20 mg/kg/d, 2 months Rifampin 600 mg/d for 4 months if there is a high probability of exposure to isoniazid-resistant TB.	No
M. avium-complex[a]	**CD4 < 50** Azithromycin 1200 mg/week Clarithromycin 500 mg bid Rifabutin 300 mg qd	Lifelong treatment
Histoplasma capsulatum[a]	**CD4 < 100, in endemic areas** Itraconazole 200 mg qd	**Previous episode of histoplasmosis** Itraconazole 200 mg bid Amphotericin B 1 mg/kg/week iv
Coccidioides immitisa	No	**Previous episode of coccidioidomycosis** Fluconazole 400 mg qd Amphotericin B 1 mg/kg/week iv Itraconazole 200 mg/12 h
Salmonella sp. (no-typhi)	No	**Episode of bacteremia** Ciprofloxacin 500 mg bid during several months
Streptococcus pneumoniae	**CD4 > 200** Antipneumococcal vaccination 0.5 mL im every 5 years. If previous dosage was applied at CD4 < 200, and with HAART it raises to >200, revaccinate	
Hepatitis B	**Negative markers for hepatitis B** Hepatitis B vaccination (3 doses)	
Influenza	**HIV +** Flu vaccination 0.5 mL/year im	

[a]Not routinely used in Spain

Table 3. *Recommendations for the simultaneous administration of antiretrovirals with rifampin or rifabutin*

Drug	With rifabutin	With rifampin	Comments
Saquinavir			
Hard gelatin capsules	Possible, if ritonavir is included in the regimen.	Possible, if ritonavir is included in the regimen.	Pharmacokinetic data and clinical experience are limited. (dose: saquinavir 400 mg bid + ritonavir 400 mg bid)
Soft gelatin capsules	Probable (dose: rifabutin 600 mg qd or 2-3 times/week or 150 mg qd or 2-3 times/week)	Possible, if ritonavir is included in the regimen.	Pharmacocinetic data and clinical experience are limited. The co-administration of saquinavir + rifampin is not recommended without ritonavir.
Ritonavir	Probable (rifabutin: 150 mg 2-3 times/week)	Probable	Pharmacokinetic data and clinical experience on the co-administration of ritonavir + rifampin are limited.
Indinavir	Yes	No	Clinical data are limited but favourable. (dose indinavir: 800 mg tid or 1000 mg tid + rifabutin 150 mg qd or 300 mg 2-3 times per week).
Nelfinavir	Yes	No	Clinical data are limited but favourable. (dose nelfinavir: 750 mg tid or 1250 mg bid or 1000 mg tid + rifabutin 150 mg qd or 300 mg 2-3 times per week).
Amprenavir	Yes	No	No clinical experience, but would be possible with the normal dose of rifabutin.
Neviparine	Yes	No	No published clinical experience. The combination would be possible with the normal dose of rifabutin.
Delavirdine	No	No	
Efavirenz	Probable *	Probable&	* There is no published clinical data. The combination is possible. (rifabutin: 450 mg or 600 mg qd, or 600 mg 2-3 times/week). & There is no published clinical experience but the combination is possible with the normal dose of rifampin + efavirenz 600 mg or 800 mg qd.

HAART regimens enable at least a partial, and often a significant, immune reconstitution in a large proportion of patients, including those who previously showed severe immunosuppression[44-47]. The EuroSIDA study showed that patients who recovered a CD4 count over 200 cells/mm³ had a much lower risk of OI compared to patients whose CD4 count remained below 50 cells/mm³, even when the nadir CD4 count had been as low as 50 cells/mm³. The risk of OI is also somewhat lower in patients whose nadir CD4 count never fell below 150 cells/mm³ compared to patients whose nadir was below this level (Fig. 3).

Although the CD4 count sometimes increases after only a few weeks on antiretroviral treatment, it is likely that at least 3-6 months or more are necessary to acquire specific responses to some infections whose memory cell clones have been lost due to immunosuppression[45]. In such cases, the time required for the recovery of naive cells, and their transformation to memory cells after contact with the antigen, makes it advisable to wait several months before discontinuing prophylactic regimens, as will be discussed later in this chapter.

Clinical manifestations of OI with HAART

The majority of OI continue to show the same clinical signs as those observed before the introduction of HAART. Nevertheless, atypical patterns have recently been described in patients receiving anti-retroviral treatment for only a few weeks or months. The immunological, inflammatory response associated with the initiation of HAART gives rise to diseases which were previously sub-clinical but which can occasionally manifest atypically[23-27].

Race *et al.*[25] described a group of five patients with CD4 < 50 cells/mm³ who after 1-3 weeks on HAART (indinavir plus one or two nucleoside analogues), presented with an episode of MAC infection consisting of high fever (>39°) leukocytosis and cervical, thoracic or abdominal adenopathies, a pattern which differs from the widespread infection generally seen in HIV infection. Several authors have documented the appearance of uveitis in patients who experience an initial episode of CMV retinitis, or who are undergoing maintenance treatment after remission of an acute episode[23,24].

Prevention of OI

When considering OI prevention, three principles must be kept in mind: 1) prevention of exposure to certain pathogens, by advising patients how to avoid contact with them, such as T. *gondii* in the case of seronegative patients. Table 1 contains a list of recommendations; 2) primary prophylaxis, which refers to the prevention of initial infectious episodes or the reactivation of latent infections; and 3) secondary prophylaxis, which refers to the prevention of disease reactivation after treatment for an acute episode.

Table 4. *Prospective studies on the discontinuation of primary prophylaxis for* Pneumocystis carinii *pneumonia in HIV-infected patients*

Study	Entry criteria	N° of patients	CD4 nadir (median) Cells/mm^3	CD4 (median) when Prophylaxix is stopped	Follow-up (months)	PCP (n° of cases)
Schneider[84]	CD4 > 200 cells/mm^3 on 2 occasions > 1 month apart, on HAART.	62	85[b]	353[b]	14[b]	0
Weverling[85]	CD4 > 200 cells/mm^3, on HAART.	236	147	312	5	0
Furrer[83]	CD4 > 200 cells/mm^3 and percentage >14% during 12 weeks of combined therapy.	262	110	325	11.3	0
Lopez[87]	CD4 > 200 cells/mm^3 and HIV-RNA < 5000 copies/mL (both during > 3months), on HAART.	274[a]	102	340	11.3	0
Dworkin[88]	CD4 > 200 cells/mm^3 with an increase of > 100/mm^3 on antiretroviral therapy.	736	150	330	9.2	3
Kirk[86]	CD4 > 200 cells/mm^3 during > 6 months, on HAART.	193	117	341	9.6	1

[a]Includes 24 patients who discontinued secondary prophylaxis.
[b]Refers to the mean rather than the median.

Primary prophylaxis

For more than a decade, primary prophylaxis regimens have been administered for some of the most common and most serious OI[7,48-55]. Despite the changes that have taken place in the treatment and evaluation of HIV infection, recommendations have remained unchanged for patients at risk of acquiring an opportunistic infection[6].

Table 2 details the drug regimens for primary and secondary prophylaxis and possible alternatives to these regimens.

In Spain, the only routinely applied prophylaxes are those for *P. carinii* pneumonia, toxoplasmosis and tuberculosis[55]. Cotrimoxazole (trimethoprim-sulfamethoxazole) continues to be the regimen of choice for the two former OI, because of its proven efficacy, easy administration, low cost and the fact that it protects against bacterial, respiratory infections and probably against other infectious agents such as Salmonella or Nocardia[7,49,51]. The most frequently used alternatives to cotrimoxazole for the simultaneous prevention of *P. carinii* pneumonia and toxoplasmosis are pyrimethamine associated with dapsone or aerosolised pentamidine[7,48-51]. The latter may be administered only if there is no risk of toxoplasmosis (negative serology to *T. gondii* or CD4 >100 cells/mm^3).

In the case of tuberculosis, several studies have documented the lack of efficacy of prophylaxis with isoniazid in anergic HIV-infected patients[56-58], and it is currently recommended only in PPD+ individuals[59,60]. It has recently been shown that a short regimen of rifampin and pirazinamide can be effective, and may be advisable in patients who would have difficulty in completing the longer isoniazid regimens[61]. If rifampin or rifabutin are administered, possible interactions with protease inhibitors and non-nucleoside reverse-transcriptase inhibitors must be taken into account (Table 3)[62].

In countries such as the USA, where MAC infection was frequent before the advent of HAART, prophylaxis against this infection is routinely administered to patients with a CD4 count <50 cells/mm^3 [63,64].

While several studies have demonstrated the efficacy of some preventive drug regimens against cryptococcosis or CMV, the inconvenience associated with these regimens, such as high cost, toxicity and, in the case of oral ganciclovir (for CMV), the inconvenient dosing, coupled with, in the case of cryptococcal infection, the low rate of infection and the possibility of facilitating the appearance of fluconazole-resistant candida strains, means they are only used in selected cases and their routine use is not recommended[65-67]. In the context of HAART, several authors have suggested that primary prophylaxis for CMV or preemptive treatment might be used as a 'bridge' for severely immunosuppressed patients who are beginning antiretroviral treatment and who are at a high risk of symptomatic CMV disease (positive antigen pp65 or PCR-CMV). This approach would provide them with protection during the initial months of treatment. Anti-CMV therapy could then be discontinued after 3-6 months if the CD4 cell count increases above 150 cells/mm^3 and HIV viral load is undetectable or considerably reduced. Unfortunately, the validity and utility of this strategy has not been demonstrated yet.

Leishmaniasis is a frequent OI in immunosuppressed HIV-infected patients in endemic geographic areas such as Spain. To date, the efficacy of a primary prophylaxis regimen has not been proven[68]. However, as with the majority of opportunistic infections, HAART is probably the best prophylaxis.

Table 5. *Studies of patients with HIV infection who discontinued secondary prophylaxis for cytomegalovirus*

Study	CD4 count (cells/mm³) entry criteria	N° of pts	CD4 (median) during retinitis (cells/mm³)	CD4 (median) when prophylaxis was stopped (cells/mm³)	Follow-up (median) (months)	CMV (n° of cases)
Whitcup[92]	>150	14	26	317	16.4 *	0
Macdonald[93]	Increase	11	42	183	5.2	0
Tural[94]	>150 **	7	35	–	9	0
Vrabec[95]	>100	8	<20	255 *	11.4 *	0
Kirk[86]	>100	5	27	179	12	0
Pérez[96]	>150	19	?	299	17	0

* Represents the mean rather than the median.
** Other criteria were: viral load < 200 copies/mL and negative CMV-PCR.

Immunisation

For many years, vaccination against certain infections has formed a routine part of the care of HIV-infected patients[69,70]. Table 2 lists the current recommendations.

Secondary prophylaxis

The majority of OI recur when treatment for an acute episode is discontinued. Patients may, therefore, continue to receive a lifelong maintenance regimen or secondary prophylaxis. This is particularly true in the case of OI such as *P. carinii* pneumonia, toxoplasmic encephalitis, CMV retinitis, cryptococcosis and MAC infection[71,76]. There is also some evidence regarding the efficacy of a maintenance regimen in the case of leishmaniasis[77]. Tuberculosis does not recur in these patients with any greater frequency than in patients from the general population and secondary prophylaxis is therefore not required. Table 2 describes the most common secondary prophylaxis drug regimens.

Advances in primary and secondary prophylaxis

P. carinii pneumonia

An American study demonstrated that an intermittent regimen of cotrimoxazole is somewhat less effective than a daily regimen in the primary prophylaxis of *P. carinii* pneumonia[78]. Nevertheless, the long demonstrated efficacy of intermittent regimens and their widespread use make the adoption of daily regimens difficult, although such regimens may be indicated in severely immunosuppressed patients at high risk of developing the disease. Even in such cases, however, it is rare for intermittent regimens of cotrimoxazole to fail. Another study of prophylaxis against *P. carinii* pneumonia demons-trated that in patients who did not tolerate cotrimoxazole, atovaquone was an effective alternative and comparable in terms of effectiveness to dapsone[79].

Toxoplasmosis

In a Spanish, multi-centre study, a regimen of sulfadiazine (1 gr bid), pyrimethamine (50 mg qd) and folinic acid (15 mg qd) three days per week was shown to be as effective as a daily regimen of sulfadiazine (1gr bid), pyrimethamine (25 mg qd) and folinic acid (15 mg qd) in the secondary prophylaxis of toxoplasmic encephalitis[72].

Citomegalovirus

Oral valganciclovir, a prodrug of ganciclovir, achieves blood drug levels equivalent to those found with intravenous administration. In a study comparing ganciclovir IV (5 mg bid) and oral valganciclovir (900 mg bid) no differences were found in the progression of retinitis, improvement of viremia or toxicity[80]. Oral valganciclovir would be the initial oral treatment of choice for CMV retinitis after the onset of an acute episode. Unfortunately, this therapy was only developed after the incidence of infection had substantially decreased.

Histoplasmosis

The results of a recent study in patients with histoplasmosis, showed that liposomal amphotericin (Ambisome) achieved a more rapid defervescence, a lower nephro-toxicity and a lower incidence of reaction to injection than conventional amphotericin B[81]. Of course, the much higher cost of liposomal treatment is a disadvantage of this therapy.

Discontinuation of primary and secondary prophylaxis for OI

As mentioned above, the partial recovery of immunity achieved by a proportion of immunosuppressed HIV-infected patients has led to debate regarding the advisability of discontinuing prophylaxis for certain OI. Initially, some small, observational studies suggested this was possible having CMV retinitis or *P. carinii* pneumonia. More recently, larger retros-pective, prospective and randomised studies have confirmed that for some OI, primary prophy-

Table 6. *Recommendations for discontinuing primary and secondary prophylaxis against opportunistic infections in HIV-infected patients.*

	Primary prophylaxis		Secondary prophylaxis	
	discontinue	restart	discontinue	restart
Pneumocystis carinii	CD4 > 200 cells/mm^3 during 3-6 months	CD4 < 200 or oral candidiasis	CD4 > 200 cells/mm^3 during 3-6 months	Same as for primary prophylaxis
Toxoplasma gondii	Same as for *P. carinii*		No data	NA*
M. avium	CD4 > 100 cells/mm^3 during 3-6 months	CD4 < 50 cells/mm^3	No data	NA*
Cytomegalovirus	NA*	NA*	CD4 >100-150 cells/mm^3 during 3-6 months **	CD4 < 50 cells/mm^3

* NA = Not applicable.
** In patients with damage not affecting vision, adequate vision in the contralateral eye and fundoscopic monitoring.

laxis, and in some cases secondary prophylaxis, may be stopped without risk of recurrence[82-97]. However, this is only possible if the patient is above the CD4 risk threshold[6]. It is also advisable to have a viral load undetectable or low and stable, since an elevated viral load would be associated with a decrease in the CD4 count in the months following discontinuation of therapy. It is important to monitor the patient at least every three months and to reinitiate the prophylaxis regimen if the conditions allowing its discontinuation have not been maintained.

P. carinii *pneumonia*

This is the most well documented infection in terms of the effects of discontinuing prophylaxis. At least six observational studies published recently suggest that primary prophylaxis for *P. carinii* pneumonia can be discontinued with very little risk (Table 4)[83-88]. The six studies collected data from a total of 1400 patients with a nadir CD4 count (the lowest count during disease evolution) ranging from 85 to 150 cells per cubic millimetre and CD4 counts from 312 to 353 at the time of inclusion in the study. After 5-14 months of follow-up, only 4 cases of *P. carinii* pneumonia were observed, three of which were from the same study.

In a large, multicentre, open-label, randomised study performed in Spain to compare the incidence of *P. carinii* pneumonia in patients continuing primary and secondary prophylaxis and those who suspended therapy, no new episodes of OI were found[87]. In the case of primary prophylaxis, data was obtained from 474 patients with mean CD4 counts of approximately 330 cells/mm^3 (nadir of 113 cells/mm^3 in the discontinuation arm) on study entry. Over 80% of these patients had viral loads <500 HIV-RNA copies/mL and patients were followed for an average of 19 months (377 patient/years in the discontinuation arm). For secondary prophylaxis, data was obtained from 133 patients with mean CD4 counts of 350 cells/mm^3 (nadir of 32 cells/mm^3 in the discontinuation arm). In this group, 86% had HIV-RNA <500 copies/mL, and patients were followed for approximately one year (65 patient/years in the discontinuation arm).

A large European study[89] provided further support for the discontinuation of secondary prophylaxis against *P. carinii* pneumonia. This prospective study included eight cohorts in which no cases of recurrence were observed in patients with CD4 counts over 200 cells/mm^3 after a mean follow-up of 236 person/years.

Toxoplasmosis

Another multicentre, open-label, randomised Spanish study demonstrated that primary, and probably secondary, prophylaxis for toxoplasmosis may be stopped in patients who have recovered partial immunity with HAART[90]. Final data from this large study, presented recently at the 40th ICAAC in Toronto, showed that after patients were randomly selected to continue or suspend primary or secondary prophylaxis (with a nadir CD4 count of about 100 cells/mm^3 and a CD4 count on entry of about 350 cells/mm^3), none of the 435 patients developed toxoplasmic encephalitis after a total follow-up of 370 years in the primary prophylaxis discontinuation arm and 31 years in the secondary prophylaxis discontinuation arm. The upper limits of the 95% confidence intervals were 98% for primary prophylaxis and 13.63% for secondary prophylaxis.

In a recent letter published in the *Lancet*, a multicentre Swiss group presented the results of an observational study on the discontinuation of primary prophylaxis in toxoplasmosis. A cohort of 199 patients received prophylaxis consisting of 88.4% cotrimoxazole for an average of 26 months[91]. The nadir CD4 count was 111 (59-150) cells/mm^3 and the CD4 count at the time of discontinuation was 340 (278-408) cells/mm^3. Overall 64% of patients had a viral load <200 copies/mL at study entry. After a total follow-up of 272 patient/years, no cases of toxoplasmosis were observed (the confidence interval for incidence in 100 patient/years was 0-1.1).

Cytomegalovirus

The evidence for the discontinuation of secondary prophylaxis for CMV is based on data from a relatively small number of patients (Table 5)[92-95]. However, the almost uniform occurrence of relapse a few weeks after discontinuation of CMV therapy in the era before HAART was immplemented, as well as the drawbacks of maintenance treatment for this infection (intravenous administration, or a large number of pills, toxicity, high cost, etc.) led the US Department of

Health and the American Society for Infectious Diseases, in their latest guidelines for OI prevention, to suggest considering discontinuation of secondary prophylaxis for CMV retinitis in patients who maintained a CD4 count above 100-150 cells/mm^3 for at least 3-6 months[6]. The decision to discontinue treatment should be taken in collaboration with an ophthalmologist, and taking into account the site of the lesion, vision in the contra-lateral eye, and the possibility of conducting a regular fundoscopic follow-up.

Infection by Mycobacterium avium *complex*

A recent American study has demonstrated that primary prophylaxis for MAC may be stopped in patients with a CD4 count over 100 cells/mm^3 [97]. The study included 520 patients whose median prior nadir CD4 count was 23 cells/mm^3, and who averaged 230 cells/mm^3 at the time of inclusion in the study. Overall, 65% of the patients had had an AIDS-defining illness, and fewer than 50% of patients had viral loads under 400-500 copies/mL. Patients were randomised to receive a prophylaxis regimen of azithromycin 1200 mg/week or placebo. Overall, 70% of the patients in each group had already received, or were in the process of receiving, anti-MAC prophylaxis on entering the study. After an average follow-up of 12 months, no episodes of MAC infection were observed (95% CI for disease incidence in each group were 1-1.5 episodes per 100 person/years). Three patients in the group receiving azithromicin and 5 in the placebo group developed bacterial pneumonia (p = 0.48).

Other infections

While several anecdotal studies exist regarding prophylactic treatment for other OI[98], and clinical experience is increasing, to date the available data remain insufficient to recommend discontinuation. Table 6 provides recommendations for discontinuation of OI prophylaxis published in 1999 by the United States Public Health Service and the Infectious Disease Society of America.

Conclusions

The outcome of HIV infection has clearly changed in recent years, and it can increasingly be considered a chronic disease. In this situation, quality of life should be one of the main objectives in the care of these patients. The possibility of discontinuing some, or all, primary and secondary prophylactic regimens is one step in this direction. It makes treatment simpler and leads to fewer adverse effects and interactions between drug therapies. The problem is far from solved, however, and the difficulties involved in ensuring adherence to treatment make it one of the Achilles heels of antiretroviral treatment. At the same time, it should be remembered that continuous prevention is the primary means of combating HIV infection and its complications, by preventing its transmission, avoiding exposure of HIV-positive persons to opportunistic pathogens, and preventing primary episodes or relapses of OI in high-risk HIV-infected patients.

References

1. Clifford D, Lane H, Laughon B *et al.* Recent advances in the management of AIDS-related opportunistic infections. Ann Intern Med 1994; 120: 945-55.
2. Gottlieb M, Schroff R, Schanker H, *et al. Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 1981; 305: 1425-31.
3. Masur H, Michele M, Greene J *et al.* An outbreak of community acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. N Engl J Med 1981; 305: 1431-8.
4. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus. MMWR 1989; 38: suppl 5): 1-9.
5. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR 1997; 46 (RR-12): 1-46.
6. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR 1999; 48 (No. RR-10).
7. Podzamczer D, Salazar A, Jiménez J *et al.* Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmosis in patients infected with HIV. Ann Intern Med 1995; 122: 755-61.
8. Gordin F, Chaisson R, Matts JP *et al.* Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial: Terry Beirn Community Programs for Clinical Research on AIDS. JAMA 2000; 283: 1445-50.
9. Drew WL, Ives D, Lalezari JP, *et al.* Oral Ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS. N Engl J Med 1995; 333:615-20.
10. Kovacs J, Masur H. Prophylaxis against opportunistic infections in patients with human immunodeficiency virus infection. N Engl J Med 2000; 342: 1416-29.
11. Masur H. Public Health Service Task Force on prophylaxis and Therapy for *Mycobacterium avium* complex disease in patients infected with human immunodeficiency virus. N Engl J Med 1993; 329: 898-904.
12. Moore R, Keruly J, Chaisson R. Decline in CMV and other opportunistic disease with combination antiretroviral therapy. Fifth Conference on Retroviruses and Opportunistic Infections. Chicago, 1998 (abstract 113).
13. Miller V, Mocroft A, Reiss P *et al.* Relations among CD4 lymphocyte count nadir, antiretroviral therapy and HIV-1 disease progression: results from the EuroSIDA study. Ann Intern Med 1999; 130: 570-7.
14. Palella F Jr, Delaney K, Moorman A *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998; 338: 853-60.
15. Hammer S, Squires K, Hughes M *et al.* A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med 1997; 337: 725-33.
16. Giorgi J, Majchrowicz M, Johnson T *et al.* Immunologic effects of combined protease inhibitor and reverse transcriptase inhibitor therapy in previously treated chronic HIV-1 infection. AIDS 1998; 12: 1833-44.
17. Kelleher A, Carr A, Zaunders J, Cooper D. Alterations in the immune response of human immunodeficiency virus infected subjects treated with an HIV specific protease inhibitor, ritonavir. J Infect Dis 1996; 173: 324-8.
18. Autran B, Carcelain G, Li T *et al.* Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. Science 1997; 277: 112-5.
19. Rosenberg E, Billingsley JM, Caliendo A *et al.* Vigorous HIV-1 specific CD4+T cell responses associated with control of viremia. Science 1997; 278: 1447-50.

20. Jones J, Hanson D, Dworkin M *et al.* Surveillance for AIDS-defining opportunistic illnesses, 1992-1997. MMWR 1999; 48 (SS-2): 1-22.

21. Mocroft A, Vella S, Benfield T *et al.* Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998; 352: 1725-30.

22. Mouton Y, Alfandari S, Valette M *et al.* Impact of protease inhibitors on AIDS-defining events and hospitalizations in 10 French AIDS reference centres. AIDS 1997; 11: F101-F105.

23. Karavellas M, Lowder C, MacDonald C *et al.* Immune recovery vitritis associated with inactive cytomegalovirus retinitis: A new syndrome. Arch Ophtalmol 1998; 116: 169-75.

24. Zegans M, Walton R, Holland G *et al.* Transient vitreous inflammatory reactions associated with combination antiretroviral therapy in patients with AIDS and cytomegalovirus retinitis. Am J Ophthalmol 1998; 125: 292-300.

25. Race E, Adelson-Mitty J, Kriegel G *et al.* Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. Lancet 1998; 351: 252-5.

26. Chien J, Johnson J. Paradoxical reactions in HIV and pulmonary TB. Chest 1998; 114: 933-6.

27. Sepkowitz K. Effects of HAART on natural history of AIDS-related opportunistic infections. Lancet 1998; 351: 228-30.

28. Brodt H, Kamps B, Gute P *et al.* Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. AIDS 1997; 11: 1731-8.

29. Law M, De Winter L, McDonald A *et al.* AIDS diagnoses at higher CD4 counts in Australia following the introduction of highly active antiretroviral treatment. AIDS 1999; 13: 263-9.

30. Fätkenheuer G, Theisen A, Rockstroh G *et al.* Virological treatment failure of protease inhibitor therapy in an unselected cohort of HIV-infected patients. AIDS 1997; 11: F113-F116.

31. Ferrer E, Consiglio E, Podzamczer D *et al.* Analysis of the discontinuation of protease inhibitor therapy in routine clinical practice. Scand J Infect Dis 1999; 31: 495-9.

32. Powderly W. Opportunistic infections. Report from the 7th Conference on Retroviruses and Opportunistic Infections. Newsline. JAMA 2000.

33. Philips A, Lee C, Elford J *et al.* Serial CD4 lymphocyte counts and development of AIDS. Lancet 1991; 337: 389-92.

34. Keet I, Krijnen P, Koot M *et al.* Predictors of rapid progression to AIDS in HIV-1 seroconverters. AIDS 1993; 7: 51-7.

35. Kaplan J, Masur H, Holmes K *et al*, and the USPHS/IDSA Prevention of Opportunistic Infections Working Group. USPHS/IDSA Guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: an overview. Clin Infect Dis 1995; 21 (suppl 1): S12-S31.

36. Mellors J, Rinaldo C, Gupta *et al.* Prognosis in HIV infection predicted by the quantity of virus in plasma. Science 1996; 272: 1167-9.

37. Engels E, Rosenberg P, O'Brien T, Goedert J. Plasma HIV viral load in patients with hemophilia and late-stage HIV disease: a measure of current immune suppression: Multicenter Hemophilia Cohort Study. Ann Intern Med 1999; 131: 256-64.

38. Lyles R, Chu C, Mellors J *et al.* Prognostic value of plasma HIV RNA in the natural history of *Pneumocystis carinii* pneumonia, *cytomegalovirus* and *Mycobacterium avium* complex. AIDS 1999; 13: 341-9.

39. Kaplan J, Hanson D, Dworkin M, Jones J. HIV plasma RNA, an independent predictor of opportunistic infections in HIV-infected persons. 39th ICAAC. San Francisco 1999 (abstract 124).

40. Crow S, Carlín J, Stewart K, Lucas C, Holy J. Predictive value of CD4 lymphocyte numbers for the development of opportunistic infections and malignancies in HIV-infected persons. J Acquir Immune Defic Syndr 1991; 4: 770-6.

41. Phair J, Muñoz A, Saah A *et al.*, Multicenter AIDS Cohort Study Group. The risk of *Pneumocystis carinii* pneumonia (letter). N Engl J Med 1990; 322: 1607-8.

42. Miró J, Buira E, Mallolas J *et al.* Linfocitos CD4+ e infecciones oportunistas y neoplasias en pacientes con infección por VIH. Med Clin (Barc) 1994; 102: 566-70.

43. Moore R, Chaisson R. Natural history of opportunistic disease in an HIV-infected urban clinic cohort. Ann Intern Med 1996; 124: 633-42.

44. Pakker N, Notermans D, De Boer R *et al.* Biphasic kinetics of peripheral blood T cells after triple combination therapy in HIV-1 infection: a composite of redistribution and proliferation. Nat Med 1998; 4: 208-14.

45. Miró J, Martínez Chamorro E, Peña J. Restauración inmunológica y tratamiento antirretroviral de gran actividad (TARGA). En: Avances en el manejo del paciente infectado por VIH. Podzamczer D (ed). Madrid: Team Pharma 1999: 152-170.

46. Connors M, Kovacs J, Krevat S *et al.* HIV infection induces changes in CD4+ cell phenotype and depletions within the CD4+ T-cell repertoire that are not immediately restored by antiviral or immune-based therapies. Nat Med 1997; 3: 533-40.

47. Gorochov G, Neumann A, Kereveur A *et al.* Perturbation of CD4+ and CD8+ T-cell repertoires during progression to AIDS and regulation of the CD4+ repertoire during antiviral therapy. Nat Med 1998; 4: 215-21.

48. Opravil M, Hirschel B, Lazzarin A *et al.* Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus infected patients. Clin Infect Dis 1995; 20: 531-41.

49. Bozzette S, Finkelstein D, Spector S *et al.* A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. N Engl J Med 1995; 332: 693-9.

50. Girard P-M, Landman R, Gaudebour C *et al.* Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in HIV infection. N Engl J Med 1993; 328: 1514-20.

51. Schneider M, Hoepelman A, Eeftinck Schattenkerk J *et al.* A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. N Engl J Med 1992; 327: 1836-41.

52. Havlir D, Dubé M, Sattler F *et al.* Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. N Engl J Med 1996; 335: 392-8.

53. Spector S, McKinley G, Lalezari J *et al.* Oral ganciclovir for the prevention of cytomegalovirus disease in persons with AIDS. N Engl J Med 1996; 334: 1491-7.

54. Powderly W, Finkelstein D, Feinberg J *et al.* A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. N Engl J Med 1995; 332: 700-5.

55. Podzamczer D, Consiglio E, Rufí G *et al.* Profilaxis primaria y secundaria de las infecciones más frecuentes e inmunización en pacientes adultos con infección por VIH. En: Gatell J, Clotet B, Podzamczer D, Miró J, Mallolas J (eds) Guía práctica del SIDA 5.ª ed. Barcelona: Masson S.A. 1998: 303-19.

56. Gordin F, Matts J, Miller C *et al.* A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. N Engl J Med 1997; 337: 315-20.

57. Whalen C, Johnson J, Okwera A *et al.* A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. N Engl J Med 1997; 337: 801-8.

58. CDC. Anergy skin testing and preventive therapy for HIV-infected persons: revised recommendations. MMWR 1997; 46 (RR-15): 1-10.

59. Pape J, Jeans S, Ho J, Hafner A, Johnson W Jr. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet 1993; 342: 268-72.

60. CDC. Prevention and treatment of tuberculosis among patients infected human immunodeficiency virus: principles of therapy and revised recommendations. MMWR 1998; 47 (no RR-20).

61. Halsey N, Coberly J, Desormeaux J *et al.* Randomised trial of isoniazid versus rifampicin and pirazinamide for prevention of tuberculosis in HIV-1 infection. Lancet 1998; 351: 786-92.

62. CDC. Guidelines for the use of Rifabutin or Rifampin for the Treatment and Prevention of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors. MMWR 2000; 49: 185-9.

63. Nightingale S, Cameron W, Gordin F *et al.* Two controlled trials of rifabutin prophylaxis against *Mycobacterium avium* complex in AIDS. N Engl J Med 1993; 329: 828-33.

64. Pierce M, Crampton S, Henry D *et al.* A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. N Engl J Med 1996; 335: 384-91.

65. Spector S, Pilcher M, Lamy P *et al.* PCR of plasma for cytomegalovirus DNA identifies HIV-infected persons most likely to benefit from oral ganciclovir prophylaxis. XI International Conference on AIDS. Vancouver 1996 (abstract ThB 302).

66. Podzamczer D, Ferrer E, Garcia A *et al.* pp65 antigenemia as a marker of future CMV disease and mortality in HIV-infected patients. Scand J Infect Dis 1997; 29: 223-7.

67. Sanguineti A, Carmichael J, Campbell K. Fluconazole-resistant *Candida albicans* after long-term suppressive therapy. Arch Intern Med 1993; 153: 1122-4.

68. Alvar J, Canavate C, Gutiérrez-Solar B *et al.* Leishmania and human immunodeficiency virus coinfection: the first 10 years. Clin Microbiol Rev 1997; 10: 298-319.

69. Ward J, Hanson D, Jones J, Kaplan J. Pneumococcal vaccination and the incidence of pneumonia among HIV-infected persons. 34th Annual Meeting of the Infectious Diseases Society of America. New Orleans, September 1996 (abstract 81).

70. Tasker S, Treanor J, Paxton W, Wallace M. Efficacy of influenza vaccination in HIV-infected persons: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999; 131: 430-3.

71. Katlama C, De Wit S, O' Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin versus pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. Clin Infect Dis 1996; 22: 268-75.

72. Podzamczer D, Miró J, Ferrer E *et al.* Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. Eur J Clin Microbiol Infect Dis 2000; 19: 89-95.

73. Drew W, Ives D, Lalezari J *et al.* Oral ganciclovir as maintenance treatment for cytomegalovirus retinitis in patients with AIDS. N Engl J Med 1995; 333: 615-20.

74. The Oral Ganciclovir European and Australian Cooperative Study Group. Intravenous versus oral ganciclovir: European/Australian comparative study of efficacy and safety in the prevention of cytomegalovirus retinitis recurrence in patients with AIDS. AIDS 1995; 9: 471-7.

75. Bozzette S, Larsen R, Chiu J *et al.* A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. N Engl J Med 1991; 324: 580-4.

76. Chaisson R, Benson C, Dube M *et al.* Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease: a randomized, double-blind, dose-ranging study in patients with AIDS. Ann Intern Med 1994; 121: 905-11.

77. Ribera E, Ocaña I, De Otero J *et al.* Prophylaxis of visceral leishmaniasis in human immunodeficiency virus-infected patients. Am J Med 1996; 100: 496-501.

78. El-Sadr W, Luskin-Hawk R, Yurik TM *et al.* A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected persons: Terry Beirn Community Programs for Clinical Research on AIDS. Clin Infect Dis 1999; 29: 775-83.

79. El-Sadr W, Murphy R, Yurik TM *et al.* Atovaquone compared for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. N Engl J Med 1998; 339: 1889-95.

80. Martin D, Sierra-Madero J, Walmsley S, Wolitz R, Brown F, Robinson C. Valganciclovir (VGCV) vs. IV ganciclovir (GCV) as induction therapy for newly diagnosed cytomegalovirus (CMV) retinitis: a randomized controlled study. 7th Conference of Retroviruses and Opportunistic Infections. San Francisco 2000; (abstract 231).

81. Johnson P, Wheat L, Cloud G *et al.* A multicenter randomized trial comparing amphotericin B (AmB) and liposomal Amphotericin B (AmBisome, LamB) as induction therapy of disseminated histoplasmosis (DH) in AIDS patients. 7th Conference of Retroviruses and Opportunistic Infections. San Francisco 2000 (abstract 232).

82. Soriano V, Dona C, Rodríguez-Rosado R, Barreiro P, González-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. AIDS 2000; 14: 383-6.

83. Furrer H, Egger M, Opravil M *et al.* Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. N Engl J Med 1999; 340: 1301-6.

84. Schneider M, Borleffs J, Stolk R, Haspers C, Hoepelman A. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. Lancet 1999; 353: 201-3.

85. Weverling G, Mocroft A, Ledergerber B *et al.* Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. Lancet 1999; 353: 1293-8.

86. Kirk O, Lundgren J, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? AIDS 1999; 13: 1647-51.

87. López J, Miró J, Peña J, Podzamczer D. Discontinuation of PCP prophylaxis is safe in HIV-infected patients after immunological recovery with HAART: results of the Gesida 04/98 study. 39th ICAAC. San Francisco 1999 (abstract 19).

88. Dworkin M, Hanson D, Jones J, Kaplan J, Adult/Adolescent Spectrum of HIV Disease Project (ASD). The risk for *Pneumocystis carinii* pneumonia (PCP) and disseminated non-tuberculous mycobacteriosis (dMb) after an antiretroviral therapy (ART) associated increase in the CD4+ T-lymphocyte count. Sixth Conference of Retroviruses and Opportunistic Infections. Chicago 1999 (abstract 198).

89. Ledergerber B, Mocroft A, Reiss P *et al.* It is safe to discontinue secondary prophylaxis for PCP in HIV-infected patients treated with HAART: results from eight prospective European cohorts. 7th Conference of Retroviruses and Opportunistic Infections. San Francisco 2000; (abstract LB5).

90. Miró J, López J, Podzamczer D *et al.* Discontinuation of primary or secondary *Toxoplasma gondii* prophylaxis is safe in HIV-1-infected patients after immunological recovery with HAART: Final results of the GESIDA 04/98-B study. 40th ICAAC. Toronto 2000. (abstract L-16).

91. Furrer H, Opravil M, Bernasconi E, Telenti A, Egger M, for the Swiss HIV Cohort Study. Stopping primary prophylaxis in HIV-1-infected patients at high risk of toxoplasma encephalitis. Lancet 2000 (letter); 355: 2217-8.

92. Whitcup S, Fortin E, Lindblad A *et al.* Discontinuation of anticytomegalovirus therapy in persons with HIV infection and cytomegalovirus retinitis. JAMA 1999; 282: 1633-7.

93. Macdonald J, Torrianti F, Morse L *et al.* Lack of reactivation of cytomegalovirus (CMV) retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4 T cells in response to highly active antiretroviral therapy. J Infect Dis 1998; 177: 1182-7.

94. Tural C, Romeu J, Sirera G *et al.* Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. J Infect Dis 1998; 177: 1080-3.

95. Vrabec T, Baldassano V, Whitcup S. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated CD4+ counts. Ophtalmology 1998; 105: 1259-64.

96. Pérez H, Zala C, Ochoa C *et al.* Absence of reactivation of cytomegalovirus (CMV) retinitis after discontinuation of CMV maintenance therapy in patients on HAART. XIII International Conference on AIDS. Durban 2000 (abstract TuOrB359).

97. El-Sadr W, Burman W, Bjorling L *et al.* Discontinuation of prophylaxis against *Mycobacterium avium* complex disease in HIV-infected patients who have a response to antiretroviral therapy. Terry Beirn Community Programs for Clinical Research on AIDS. N Engl J Med 2000; 342: 1085-92.

98. Aberg J, Price R, Heeren D, Pearce R, Bredt B. Discontinuation of antifungal therapy for cryptococcosis after immunologic response to antiretroviral therapy. In: Program and abstracts of the 7th Conference of Retroviruses and Opportunistic Infections. San Francisco 2000 (abstract 250).