

Prophylaxis of *Pneumocystis carinii* pneumonia: too much of a good thing?

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Introductory articles

Efficacy of azithromycin in prevention of *Pneumocystis carinii* pneumonia: a randomised trial

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Background. Azithromycin in combination with sulphonamides is active against *Pneumocystis carinii* (PCP) in animals. We assessed the clinical efficacy of azithromycin for PCP prophylaxis in human beings. **Methods.** We identified HIV-1-infected patients with PCP during a prospective randomised trial comparing azithromycin, rifabutin, and the two drugs in combination for prevention of disseminated *Mycobacterium avium* infection. Patients had CD4-cell counts less than 100/ μ L at entry and received PCP prophylaxis according to the standard practice of their clinician. Analysis was by intention to treat. **Findings.** Patients receiving azithromycin, either alone ($n=233$) or in combination with rifabutin ($n=224$), had a 45% lower risk of developing PCP than those receiving rifabutin alone ($n=236$; $p=0.008$). Compared with rifabutin alone, hazard ratio for azithromycin was 0.54 (95% CI 0.32–0.94), for azithromycin plus rifabutin was 0.55 (0.32–0.94), and for regimens containing azithromycin was 0.55 (0.35–0.86). The most common side-effects involved the gastrointestinal tract with dose-limiting toxicities, and were mainly seen in patients receiving combination therapy. **Interpretation.** Azithromycin as prophylaxis for *M avium* complex disease provides additional protection against *P carinii* over and above that of standard PCP prophylaxis. Use of azithromycin is beneficial only as primary prophylaxis. (*Lancet* 1999;354:891–5)

Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection

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Background. Highly active antiretroviral therapy (HAART) has improved rates of CD4-lymphocyte recovery and decreased the incidence of HIV-1-related morbidity and mortality. We assessed whether prophylaxis against *Pneumocystis carinii* pneumonia (PCP) can be safely discontinued after HAART is started. **Methods.** We investigated 7333 HIV-1-infected patients already enrolled in EuroSIDA, a continuing prospective observational cohort study in 52 centres across Europe and Israel. We did a person-years analysis of the rate of discontinuation of PCP prophylaxis and of the incidence of PCP after the introduction of HAART into clinical practice from July, 1996. **Findings.** The rate of discontinuation of primary and secondary PCP prophylaxis increased up to 21.9 discontinuations per 100 person-years of follow-up after March, 1998. 378 patients discontinued primary (319) or secondary (59) prophylaxis a median of 10 months after starting HAART. At discontinuation for primary and secondary prophylaxis, respectively, the median CD4-lymphocyte counts were 274 cells/ μ L and 270 cells/ μ L, the median plasma HIV-1 RNA load 500 copies/mL, and the median lowest recorded CD4-lymphocyte counts 123 cells/ μ L and 60 cells/ μ L. During 247 person-years of follow-up, no patient developed PCP (incidence density 0 [95% CI 0–1.5]). **Interpretation.** The risk of PCP after stopping primary prophylaxis, especially in patients on HAART with a rise in CD4-lymphocyte count to more than 200 cells/ μ L, is sufficiently low to warrant

discontinuation of primary PCP prophylaxis. Longer follow-up is needed to confirm a similarly low risk for stopping secondary PCP prophylaxis. (*Lancet* 1999;**353**:1293–8)

Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy

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Background. It is unclear whether primary prophylaxis against *Pneumocystis carinii* pneumonia can be discontinued in patients infected with the human immunodeficiency virus (HIV) who are successfully treated with combination antiretroviral therapy. We prospectively studied the safety of stopping prophylaxis among patients in the Swiss HIV Cohort Study. **Methods.** Patients were eligible for our study if their CD4 counts had increased to at least 200 cells per cubic millimeter and 14 percent of total lymphocytes while they were receiving combination antiretroviral therapy, with these levels sustained for at least 12 weeks. Prophylaxis was stopped at study entry, and patients were examined every three months thereafter. The development of *P. carinii* pneumonia was the primary end point, and the development of toxoplasmic encephalitis the secondary end point. **Results.** Of the 262 patients included in our analysis, 121 (46.2 percent) were positive for IgG antibodies to *Toxoplasma gondii* at base line. The median CD4 count at study entry was 325 per cubic millimeter (range, 210 to 806); the median nadir CD4 count was 110 per cubic millimeter (range, 0 to 240). During a median follow-up of 11.3 months (range, 3.0 to 18.8), prophylaxis was resumed in nine patients, and two patients died. There were no cases of *P. carinii* pneumonia or toxoplasmic encephalitis. The one-sided upper 99 percent confidence limit for the incidence of *P. carinii* pneumonia was 1.9 cases per 100 patient-years (based on 238 patient-years of follow-up). The corresponding figure for toxoplasmic encephalitis was 4.2 per 100 patient-years (based on 110 patient-years of follow-up). **Conclusions.** Stopping primary prophylaxis against *P. carinii* pneumonia appears to be safe in HIV-infected patients who are receiving combination antiretroviral treatment and who have had a sustained increase in their CD4 counts to at least 200 cells per cubic millimeter and to at least 14 percent of total lymphocytes. (*N Engl J Med* 1999;**340**:1301–6)

The fungal pathogen *Pneumocystis carinii* was first described by Chagas in 1909 but its clinical importance was not recognised until 1951 when it was identified as the cause of interstitial plasma cell pneumonia, which had been described in Europe in the late 1930s and 1940s in premature and malnourished children. In the 1960s *P. carinii* pneumonia occurred mainly in children with congenital defects of the immune system and in both adults and children with acquired immune defects due to malignancy or its treatment.^{1,2} With the advent of organ transplantation, it became clear that *P. carinii* pneumonia was associated with the immunosuppression used to prevent organ rejection. With prophylaxis, case rates fell in these populations. In 1980 *P. carinii* pneumonia was the first opportunistic infection to be associated with HIV infection, and the AIDS pandemic was defined.³

Who gets *P. carinii* pneumonia?

Most cases of *P. carinii* pneumonia occur in patients with abnormalities of T lymphocyte function or numbers: *P. carinii* pneumonia rarely occurs in patients with isolated B cell defects. Before the introduction of prophylaxis, attack rates for *P. carinii* pneumonia varied from 22–43% in children with acute lymphoblastic leukaemia⁴ and 27–42% in children with severe combined immunodeficiency, to 25% in those with rhabdomyosarcoma.^{2,4} In patients who do not receive prophylaxis after organ transplantation, attack rates for *P. carinii* pneumonia vary from 4–10% following renal transplantation to 16–43% following heart or heart/lung transplantation.^{2,4} Several studies in non-HIV infected

patients have suggested, regardless of the nature of the underlying immunosuppression, that glucocorticoids are an independent risk factor for development of *P. carinii* pneumonia.^{2,5}

In HIV infected patients the CD4+ T lymphocyte count is used in clinical practice both to determine the risk of *P. carinii* pneumonia in an individual patient and to make recommendations about when to start prophylaxis (see below).^{6–10} There is increasing evidence that the CD4+ T lymphocyte count may also be useful in determining whether non-HIV infected immunosuppressed individuals are at risk of *P. carinii* pneumonia.^{11,12}

Who should receive prophylaxis?

The United States Public Health Service and the Infectious Diseases Society of America have made the following recommendations.

HIV infected patients, including those who are pregnant and those receiving combination antiretroviral therapy (also known as highly active antiretroviral therapy or HAART), should receive primary prophylaxis against *P. carinii* pneumonia if they have a CD4+ T lymphocyte count of <200 cells/ μ l or a history of oral/pharyngeal candidiasis.¹⁰ Prophylaxis should also be given to patients who have a CD4+ T lymphocyte count which is <14% of the total lymphocyte count or a history of an AIDS defining illness – for example, Kaposi's sarcoma.¹⁰ If it is not possible to monitor the CD4+ T lymphocyte count frequently (at least every three months), then consideration should be given to starting prophylaxis in patients whose CD4+ T lymphocyte

counts are between 200 and 250 cells/ μl .^{10,13} Secondary prophylaxis should be given to all HIV infected patients who have had an episode of *P. carinii* pneumonia, regardless of their CD4+ T lymphocyte count. Although HAART may cause a rise in the CD4+ T lymphocyte count to >200 cells/ μl , there are insufficient data to recommend stopping secondary prophylaxis against *P. carinii* pneumonia (see below).¹⁰

In the non-HIV infected immunosuppressed population, those with high attack rates for *P. carinii* pneumonia should receive prophylaxis.² Sepkowitz *et al* have suggested that, in addition, patients with any immune dysfunction induced by an inflammatory disease or by radiotherapy or chemotherapy who receive 20 mg/day of prednisolone (or equivalent) should receive prophylaxis.^{4,14}

What drug regimen is preferred for prophylaxis?

Co-trimoxazole 960 mg once daily is the regimen of choice for prophylaxis of *P. carinii* pneumonia in both HIV infected and non-HIV infected immunosuppressed individuals.^{9,10,15} Alternative agents which, in HIV infected patients, have been shown to be less effective include dapsone (with or without pyrimethamine),¹⁶ nebulised pentamidine,¹⁷ and atovaquone.¹⁸

The ideal agent for prophylaxis is cheap, readily available, effective, easily administered so that compliance is maintained, has low toxicity, and does not interact adversely with HAART or chemotherapy/immunosuppressive drug regimens. An additional benefit would be for it to provide "cross prophylaxis" against other micro-organisms. Cross prophylaxis is demonstrated clearly for co-trimoxazole at a dose of 960 mg once daily. In addition to effectively preventing *P. carinii* pneumonia, co-trimoxazole also protects against cerebral toxoplasmosis^{17,19} and some bacterial infections.^{17,20} Lower doses of co-trimoxazole such as 480 mg once daily²¹ or 960 mg three times a week²² are also effective regimens for prophylaxis and may also confer cross prophylaxis. Immunosuppressed HIV non-infected patients with antibodies to *Toxoplasma gondii* should not receive nebulised pentamidine as prophylaxis because of the risk of development of cerebral toxoplasmosis.^{2,19}

What are the long term benefits of prophylaxis?

The widespread availability and uptake of co-trimoxazole and other agents as prophylaxis has had a major impact on the incidence of *P. carinii* pneumonia. In one study in London *P. carinii* pneumonia accounted for 23% of all admissions to a specialist HIV unit in 1986–7 (before prophylaxis was used) but was responsible for only 13% of admissions in 1990–1 (by which time prophylaxis had been introduced).²³ Using data from 90 HIV centres in the USA, the Centres for Disease Control and Prevention, Atlanta found a reduction in the incidence of *P. carinii* pneumonia from 9.0 per 100 person years in 1991 to 5.3 per 100 person years in 1996.²⁴ Prophylaxis has also had an impact on survival time in patients with HIV infection and CD4+ T lymphocyte counts of <200 cells/ μl . In a study from San Francisco the median survival increased from 28.4 months in patients studied between 1983 and 1986 to 38.1 months in those studied between 1988 and 1993.²⁵ The largest increase in survival time was seen in those who had *P. carinii* pneumonia, suggesting that prophylaxis and treatment of this infection were important

factors in longer survival.²⁵ It is important to remember that these benefits from prophylaxis were reported before the advent of HAART.

What are the costs of prophylaxis?

The cost of prophylaxis varies considerably from £20 (US\$60) per year for co-trimoxazole to £6346 (US\$10 647) per year for atovaquone.

What adverse events are associated with prophylaxis?

Adverse reactions to co-trimoxazole, consisting of rash and/or fever, occur more commonly in patients immunosuppressed by HIV infection than in those immunosuppressed by other causes or those with normal immunity.²⁶ An explanation for this difference is not apparent. Hypotheses include HIV induced immunopathogenic effects or changes in acetylator dependent metabolism of co-trimoxazole to toxic (hydroxylamine) metabolites.²⁷ Desensitisation to co-trimoxazole should be attempted before considering a change to alternative, less effective prophylaxis.^{28,29}

What effect does long term prophylaxis have on other pathogens?

As co-trimoxazole is a potent broad spectrum antibacterial agent in addition to being the most effective agent for prophylaxis of *P. carinii* pneumonia, concerns have been expressed that its widespread long term use may lead to selection of resistance in bacteria. Until recently, once prophylaxis with co-trimoxazole was started, it was recommended that it should be used for the rest of the HIV infected person's life. It has been suggested that resistant bacteria might develop in these individuals and subsequently spread into the general population. In the non-HIV infected population there is already evidence that co-trimoxazole, used as prophylaxis in patients with acute leukaemia, may induce plasmid type resistance in Enterobacteriaceae.³⁰ In patients with HIV infection the use of co-trimoxazole has been associated with the development of co-trimoxazole resistant *Streptococcus pneumoniae*.^{31,32}

A serial cross sectional study from San Francisco General Hospital, USA has examined rates of resistance to co-trimoxazole among isolates of *Staphylococcus aureus* and also among seven common genera of the Enterobacteriaceae (including *Escherichia coli* and *Klebsiella* spp) from HIV infected and non-infected inpatients and outpatients.³³ The study period was from 1988 until 1995. At the start of the study period co-trimoxazole was not commonly used as nebulised pentamidine was the preferred option for prophylaxis, but co-trimoxazole subsequently became first choice for prophylaxis. Overall resistance rates (in all eight genera combined) were between 2.8% and 5.5% before 1988 and have risen steadily from 7.2% in 1988 to 20.4% in 1995.³³ This trend was most apparent among HIV infected patients in whom overall resistance increased from 6.3% in 1988 to 53% in 1995. The largest increases in resistance were in isolates of *S. aureus* (from 0% in 1988 to 48% in 1995) and *E. coli* (from 24% to 74%) from HIV infected patients. These data have implications for the clinician, as the long term benefit of co-trimoxazole needs to be balanced against its effect on resistance. Despite the limitations of this study (it did not control for possible influences of concomitant therapies and the study groups were incompletely defined), its findings have

led to a reduction in the use of co-trimoxazole for prophylaxis and treatment of infections other than *P carinii* pneumonia at San Francisco General Hospital.³³

Can *P carinii* become resistant to prophylaxis?

Conventional methods of determining drug resistance cannot be used to answer this question as human derived *P carinii* cannot be cultured reliably in vitro. The drug target for sulphamethoxazole (and for dapsone, which is a sulphone) is dihydropterate synthase (DHPS) and for trimethoprim is dihydrofolate reductase (DHFR); these are sequential enzymes in the metabolism of folate. In several bacteria, including *E coli*, *Neisseria meningitidis*, and *S pneumoniae*, and in the protozoan *Plasmodium falciparum*, point mutations within conserved regions of the DHPS gene confer resistance to sulphonamides.^{34–36} In *P carinii* DHPS is part of a trifunctional protein, along with dihydroneopterin aldolase and hydroxymethyl-dihydropterin pyrophosphokinase – two other enzymes in the folic acid metabolic pathway.³⁷

The first evidence of mutations in the DHPS gene of *P carinii* came from case reports³⁸ and a study of 27 patients.³⁹ Development of resistance was suggested by the finding of non-synonymous single base pair polymorphisms (point mutations) within a highly conserved region of the DHPS gene of *P carinii* resulting in amino acid substitutions at codons 55 and 57.³⁹ These amino acid substitutions are at or near to the sulpha binding sites and are homologous to mutations which cause resistance to sulpha drugs in other pathogens such as *E coli*.⁴⁰ Mutations in the *P carinii* DHPS gene were identified in seven of 27 patients and were more commonly seen in HIV infected patients with *P carinii* pneumonia who had failed co-trimoxazole or dapsone prophylaxis.³⁹ The common “wild type” DHPS of *P carinii* contains threonine at codon 55 and proline at codon 57. Single mutations are seen with threonine → alanine (codon 55) and proline → serine (codon 57). A “double mutant” exists when both amino acid substitutions occur in the same sample.

Although strongly suggestive of sulpha resistance, these data do not prove that the sequence polymorphisms confer drug resistance.⁴⁰ Stronger evidence comes from Mei *et al* who reported two patients who developed *P carinii* pneumonia while on co-trimoxazole prophylaxis.³⁹ Treatment with high dose co-trimoxazole was ineffective in one and this patient recovered when treatment was changed to pentamidine. The other patient, despite recovery with co-trimoxazole, had two further episodes of *P carinii* pneumonia. Both patients had “double mutant” DHPS genes.³⁹

Helweg-Larsen *et al* studied bronchoscopic alveolar lavage samples from 152 episodes of *P carinii* pneumonia in 144 patients from a prospective cohort in Copenhagen, Denmark and assessed, firstly, whether mutations in the DHPS gene of *P carinii* were associated with prior exposure to sulpha drugs and, secondly, whether DHPS mutations influenced outcome from *P carinii* pneumonia.⁴¹ A portion of the DHPS gene was analysed using PCR and sequencing; “wild type” *P carinii* DHPS was found in 121 episodes (79.6%) and DHPS mutations in 31 episodes (20.4%).⁴¹ The three month survival was significantly lower in patients with *P carinii* pneumonia and DHPS containing mutations than in patients with “wild type” DHPS. Factors such as low CD4+ T lymphocyte count, hypoxaemia, and older age have all been shown to be associated with a poor outcome from *P carinii* pneumonia. Even after adjustment for these prognostic variables, patients with

“mutant” DHPS *P carinii* pneumonia were three times more likely to die than those with “wild type” (hazard ratio = 3.1; 95% CI 1.2 to 8.1).⁴¹

Of note, DHPS mutations were not always associated with a failure to respond to co-trimoxazole as high dose co-trimoxazole was successful in 12 of 19 episodes with “mutant” DHPS.⁴¹ This observation suggests that strains of *P carinii* with only one or two DHPS mutations are only partially resistant to sulpha drugs.⁴⁰ In *E coli* mutations in DHPS are associated with a low level of resistance to sulpha drugs; as additional mutations accumulate, high level resistance develops.⁴² It is conceivable that the same phenomena may be occurring in *P carinii*.

In contrast, there appears to be no evidence for development of mutations in the DHFR gene of *P carinii* in patients who have received co-trimoxazole or dapsone.⁴³ In a recent study from the National Institutes of Health, Bethesda, USA the DHFR gene of human derived *P carinii* was cloned and sequenced, and evidence of both DHPS and DHFR mutations was sought in 37 isolates of *P carinii* from 35 patients.⁴³ Although 15 patients had previously received trimethoprim (in co-trimoxazole), all isolates had identical DHFR sequences apart from one isolate which had a synonymous polymorphism (which did not result in a substitution of the derived amino acid). By contrast, 16 of 37 samples had non-synonymous DHPS polymorphisms (“mutant” type DHPS) which was associated with prior use of co-trimoxazole/dapsone prophylaxis.⁴³ These results suggest that there is less selective pressure from drug exposure on DHFR than on DHPS. Although co-trimoxazole is routinely given to patients, there is little evidence from animal models of *P carinii* pneumonia that the trimethoprim component adds to the efficacy of sulphamethoxazole.^{44,45}

The drug target of atovaquone is the ubiquinone binding sites in cytochrome b of *P carinii*. Compared with co-trimoxazole, atovaquone is used much less commonly for the prophylaxis and treatment of *P carinii* pneumonia; however, non-synonymous sequence polymorphisms have been identified in the cytochrome b gene of *P carinii* from patients with prior exposure to atovaquone.⁴⁶ This suggests that *P carinii* may become resistant to other drugs.

A strategy of reducing or preventing the emergence of sulpha resistance in *P carinii* by using other agents for prophylaxis (“drug switching”) is hampered by the availability of other equally effective drugs. The impact of HAART (see below) will certainly reduce the size of the pool of HIV infected patients exposed to sulpha drugs for long periods, but this class of drug will continue to be used widely in those patients immunosuppressed by other causes.² Prevention of development of atovaquone resistance in *P falciparum* is achieved by combining it with proguanil.⁴⁶ Perhaps, if atovaquone is used for prophylaxis of *P carinii* pneumonia, it should be combined with another drug such as pyrimethamine to hinder development of resistance. The sordarins which target fungal translation-elongation factor 2 and inhibit fungal protein synthesis are active in vitro against a range of fungi⁴⁷ and in the animal model of *P carinii* pneumonia. As yet, the efficacy of sordarins in human *P carinii* pneumonia has not been studied.

Does azithromycin have activity against *P carinii*?

Animal data suggest that macrolide antibiotics, in addition to activity against bacteria and mycobacteria, also

have activity against *P. carinii*. Studies using the animal model of *P. carinii* pneumonia (the dexamethasone immunosuppressed rat) also show that combinations of sulphonamide and macrolides (erythromycin, clarithromycin and azithromycin) are active against *P. carinii* and that these combinations are possibly synergistic.⁴⁸

In the first introductory article by Dunne *et al*⁴⁹ azithromycin given in a dose of 1200 mg once weekly, with or without rifabutin 300 mg daily, was superior to rifabutin alone when given for prophylaxis of disseminated *Mycobacterium avium* complex (dMAC) in a double blind randomised trial of 693 patients with HIV infection and median CD4+ T lymphocyte counts of <40 cells/ μ l. Although the study was powered to show a difference between treated groups in prevention of dMAC, it also had 80% power to detect a 33% reduction in *P. carinii* pneumonia at a significance level of 0.05. Overall, in this study 185 patients (26.7%) had a previous episode of *P. carinii* pneumonia at entry. All patients continued their *P. carinii* prophylaxis (co-trimoxazole 58.7%, dapson 18.6%, pentamidine 17%, combinations of drugs 3.3%, none 2.6%) in addition to receiving azithromycin alone (233 patients) or with rifabutin (224 patients) or rifabutin alone (236 patients). Median follow up was 514 days and 78 patients had 85 episodes of *P. carinii* pneumonia, 48 of which (56%) were first episodes. Twice as many episodes of *P. carinii* pneumonia per 100 patient years were reported in patients receiving rifabutin alone than in those receiving azithromycin, with or without rifabutin ($p=0.008$).⁴⁹ Two important observations arise from this study. Firstly, the benefit of azithromycin in providing additional protection against *P. carinii* pneumonia was seen only in the 508 patients who were taking primary prophylaxis and not in the 185 with a past history of *P. carinii* pneumonia – that is, those receiving secondary prophylaxis. However, the numbers of patients in this subgroup were small so there was insufficient power to detect whether there was a true difference. Secondly, the lowest rates of *P. carinii* pneumonia were seen in those who received prophylaxis with co-trimoxazole or dapson.⁴⁹

Interpretation of the study data suggests a possible synergism between azithromycin and sulpha drugs. However, activity from azithromycin alone was demonstrated as, in the patients who did not receive co-trimoxazole or dapson, fewer cases of *P. carinii* pneumonia were seen in those who received azithromycin than in those who received rifabutin.⁴⁹ The authors hypothesise that an alternative explanation for their observations might be that rifabutin in fact increases the risk of *P. carinii* pneumonia, although this suggestion is not borne out by their data as the incidence (attack rate) of *P. carinii* pneumonia was similar in those receiving azithromycin alone and azithromycin with rifabutin. A drug-drug interaction remains a possible explanation. Although no experimental data exist for a drug-drug interaction between rifabutin and sulphamethoxazole or dapson, there is a significant interaction between rifampicin and dapson with the former drug producing a 7–10 fold reduction in dapson levels, rendering it ineffective.^{50,51}

What is the impact of HAART?

Several recent studies have shown that the introduction of HAART has had a significant impact on the prognosis of patients with HIV infection. These studies have shown reductions in the incidence of several op-

portunistic infections – including *P. carinii* pneumonia, dMAC, and cytomegalovirus retinitis – admissions to hospital, and overall mortality from HIV infection.^{52,53}

These benefits have occurred over and above that gained by prophylaxis of specific opportunistic infections alone. During the time of these studies the marked reductions in the incidence of opportunistic infections occurred when there was no major change in uptake of prophylaxis by patients, nor were there changes to the US Public Health Service/Infectious Diseases Society of America guidelines for the use of prophylaxis to prevent opportunistic infections in patients with HIV infection.⁵⁴ HAART brings about a rapid decrease in plasma HIV RNA and an increase in peripheral blood CD4+ T lymphocyte counts within a few weeks in most patients. The resulting “partial immune reconstitution” is shown initially by a largely clonal expansion of memory CD4+ T lymphocytes. Subsequently there is death of activated CD4+ T lymphocytes and increases in naive CD4+ T lymphocytes are seen with an expansion in the diversity of the T lymphocyte repertoire. It is unclear just how much CD4+ T lymphocyte function is restored by HAART induced partial immune reconstitution. Some researchers report a return to normal of cell mediated immunity against opportunistic pathogens such as cytomegalovirus and *Mycobacterium tuberculosis* within 3–6 months of commencing HAART.^{56,57}

The observation that HAART gives additional protection over and above that derived from specific prophylaxis for *P. carinii* led several groups to question whether prophylaxis could be safely discontinued in patients who had HAART induced partial immune reconstitution. Results from four observational cohort studies (including the introductory articles by Weverling *et al*⁵⁸ and Furrer *et al*⁵⁹) and one retrospective case control study provide evidence to support stopping primary *P. carinii* prophylaxis in HIV infected patients who have had partial immune reconstitution with HAART.^{58–62}

The study by Weverling *et al*⁵⁸ was carried out on 7333 HIV infected patients from 52 centres in Europe and Israel who were participating in the EUROSIDA study. The study aimed to describe the incidence of *P. carinii* pneumonia within the EUROSIDA cohort and to see how this had changed with time; it also aimed to describe the incidence of *P. carinii* pneumonia following the widespread introduction of HAART after July 1996 in those who discontinued *P. carinii* prophylaxis.⁵⁸ The overall incidence of *P. carinii* pneumonia fell from 49 cases per 100 person years of follow up before March 1995 to 0.3 cases per 100 person years after March 1998. Three hundred and seventy eight patients discontinued *P. carinii* prophylaxis after starting HAART; 319 (84%) had received primary prophylaxis and 59 (16%) were receiving secondary prophylaxis. The median CD4+ T lymphocyte count at the time prophylaxis was discontinued was 274 cells/ μ l (primary) and 270 cells/ μ l (secondary). Overall, the median HIV-1 RNA load was 500 copies/ml at the time prophylaxis was discontinued. However, 98 patients (26%) discontinued *P. carinii* prophylaxis with CD4+ T lymphocyte counts of <200 cells/ μ l and a median HIV-1 RNA load of 3311 copies/ml. In those with CD4+ T lymphocyte counts of <200 cells/ μ l and an HIV-1 RNA load of <500 copies/ml at the time prophylaxis was discontinued, the withdrawal of prophylaxis occurred a median of eight months (primary) and five months (secondary) after starting HAART.⁵⁸ No cases of *P. carinii* pneumonia were seen during 247 person years of follow up, irrespective of the last CD4+ T lymphocyte count/HIV-1 RNA load

at the time of stopping *P carinii* prophylaxis, the lowest ever (nadir) CD4+ T lymphocyte count before HAART was started, or the duration of HAART. Of note, there were also no cases of cerebral toxoplasmosis and only one case of recurrent bacterial pneumonia was seen, in a patient with a CD4+ T lymphocyte count of >300 cells/ μ l.⁵⁸

The study by Furrer *et al* from the Swiss HIV cohort included patients from seven treatment centres.⁵⁹ Two hundred and sixty three patients receiving *P carinii* prophylaxis who had sustained increases in CD4+ T lymphocyte counts to >200 cells/ μ l or a CD4+ :total lymphocyte ratio of >14% for three months or more after starting HAART were included in the study. The primary end point was development of *P carinii* pneumonia and the secondary end point was development of cerebral toxoplasmosis. The median CD4+ T lymphocyte count at entry was 325 cells/ μ l and the median nadir count had been 110 cells/ μ l. No *P carinii* pneumonia or cerebral toxoplasmosis occurred during the follow up period (median 11.3 months, range 3.0–18.8). Nine patients resumed prophylactic treatment, because the CD4+ T lymphocyte count fell to <200 cells/ μ l in seven cases, because of recurrent bacterial chest infection in one, and in one for personal reasons.

The study by Schneider *et al*⁶⁰ from Utrecht, Netherlands examined the incidence of *P carinii* pneumonia after discontinuation of prophylaxis (both primary and secondary) if CD4+ T lymphocyte counts were >200 cells/ μ l documented on two occasions at least one month apart after starting HAART. The study end point was development of *P carinii* pneumonia. Seventy eight patients discontinued prophylaxis (primary = 62 patients) at which time their median CD4+ T lymphocyte count was 347 cells/ μ l. Their median nadir count before starting HAART was 79 cells/ μ l. HIV-1 RNA was not detectable in 61 patients and was 15 000 copies/ml in the other 17. Prophylaxis was discontinued at a mean (SD) of 9.8 (6.4) months after starting HAART. No patients developed *P carinii* pneumonia during mean (SD) follow up of 12.7 (7.8) months.⁶⁰

In December 1997 guidelines for discontinuing prophylaxis were changed at four major AIDS centres in Denmark. Kirk *et al* studied 219 consecutive patients who stopped *P carinii* prophylaxis (primary prophylaxis in 193 patients) when their CD4+ T lymphocyte counts rose above 200 cells/ μ l for more than six months in response to HAART.⁶¹ As a group, the mean nadir CD4+ T lymphocyte had been 117 cells/ μ l (primary prophylaxis) and <50 cells/ μ l (secondary prophylaxis). One person developed *P carinii* pneumonia after 174 person years of follow up, an overall incidence of *P carinii* pneumonia of 0.6 cases per 100 person years

(95% CI 0.0 to 3.2).⁶¹ This patient had been on HAART for 1.7 years and had stopped co-trimoxazole prophylaxis five months previously. At this time the CD4+ T lymphocyte count had been 216 cells/ μ l and the HIV-1 RNA load was 40 000 cells/ μ l. The CD4+ T lymphocyte count had fallen to 143 cells/ μ l at the time of presentation with *P carinii* pneumonia. For two months before developing *P carinii* pneumonia this patient had received G-CSF. The anti-inflammatory effects of G-CSF may well have contributed to the occurrence of *P carinii* pneumonia in this case.⁶¹

Rodriguez-Guardado *et al* retrospectively compared HIV infected patients who had evidence of HAART induced partial immune reconstitution with rises in CD4+ T lymphocyte counts to >200 cells/ μ l.⁶² Twenty six patients discontinued prophylaxis against *P carinii* pneumonia and 27 continued prophylaxis. The two groups were similar in terms of HIV risk factor, type of prophylaxis and regimens of HAART, and mean CD4+ T lymphocyte count. In those who stopped prophylaxis the mean CD4+ T lymphocyte count was 310 (range 216–486) cells/ μ l. Cases were followed for a mean of 291 days; no cases of *P carinii* pneumonia were seen.

On the basis of these data the United States Public Health Service/Infectious Diseases Society of America now recommend that primary prophylaxis can be safely discontinued in patients responding to HAART with sustained increases in CD4+ T lymphocyte counts above 200 cells/ μ l.¹⁰ The guidelines acknowledge, firstly, that data to support the recommendations come largely from patients who began HAART which included a protease inhibitor, secondly, that the median follow up was 6–12 months and the median CD4+ T lymphocyte count at the time prophylaxis was discontinued was >300 cells/ μ l and, thirdly, that many of the patients who discontinued prophylaxis had a sustained suppression of HIV-1 RNA load to below detection limits of available assays.¹⁰

What if, despite HAART, CD4+ T lymphocyte counts fall below 200 cells/ μ l and/or HIV-1 RNA increases again? Current recommendations are that, in the absence of data from prospective observational studies or randomised trials, the same criteria should be used as for starting primary *P carinii* prophylaxis (see above).¹⁰ Implicit in these recommendations is the need for close patient monitoring to detect rapidly any fall in CD4+ T lymphocyte count or increase in HIV-1 RNA load which identify recurrence of a risk of *P carinii* pneumonia in individual patients. In this situation *P carinii* pneumonia must be considered in the differential diagnosis for every patient presenting with respiratory symptoms.

There are no data to support discontinuation of sec-

LEARNING POINTS

- * Co-trimoxazole 960 mg once daily is the regimen of choice for prophylaxis of *P carinii* pneumonia in both HIV infected and non-HIV infected immunosuppressed individuals
- * Long term use of co-trimoxazole as prophylaxis is associated with development of resistance in bacteria
- * Drug resistance may be developing in *P carinii*
- * Primary prophylaxis of *P carinii* pneumonia may be discontinued in patients responding to HAART with sustained increases in CD4+ T lymphocyte counts of >200 cells/ μ l. If CD4+ T lymphocyte counts fall again despite HAART, primary prophylaxis should be restarted

ondary prophylaxis, largely because of the small numbers of such patients in the above mentioned studies,⁵⁸⁻⁶² even though the HIV infected patient with HAART induced partial immune reconstitution might theoretically be at a low risk of *P carinii* pneumonia. Despite the lack of data, many physicians are now discontinuing secondary prophylaxis. This patient group requires close monitoring if this strategy is followed.

Conclusion

Prophylaxis of at risk immunosuppressed individuals effectively reduces the attack rate of *P carinii* pneumonia. Co-trimoxazole is the regimen of first choice for prophylaxis. With long term use of co-trimoxazole for prophylaxis there is evidence for the emergence of resistance in other micro-organisms as well as in *P carinii* itself. Strategies to limit lifetime exposure to co-trimoxazole are limited by the lack of other equally effective agents. Primary prophylaxis against *P carinii* pneumonia may safely be discontinued in HIV infected patients with sustained evidence of partial immune reconstitution. These patients require close follow up in order that prophylaxis may be re-started if CD4+ T lymphocyte counts fall or HIV-1 RNA load increases.

The spectre of multidrug resistant HIV is looming. In this patient population, and also in the ever increasing population of HIV non-infected immunosuppressed, the need for prophylaxis of *P carinii* will continue. There is now a pressing need for development of investigational drugs as alternative agents against *P carinii* and other opportunistic infections.

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