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DISCONTINUATION OF PRIMARY PROPHYLAXIS AGAINST *PNEUMOCYSTIS CARINII* PNEUMONIA IN HIV-1–INFECTED ADULTS TREATED WITH COMBINATION ANTIRETROVIRAL THERAPY

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ABSTRACT

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.)

FOR many years *Pneumocystis carinii* pneumonia has been the most frequent event defining the presence of the acquired immunodeficiency syndrome (AIDS) among adults in developed countries who are infected with the human immunodeficiency virus (HIV).[1,2] *P. carinii* pneumonia is associated with considerable morbidity and mortality[3,4]; it occurs predominantly in patients in whom the number of CD4-positive lymphocytes has fallen below 200 per cubic millimeter, with an estimated incidence of 20 cases per 100 patient-years.[5,6] Several studies have shown that primary prophylaxis with trimethoprim–sulfamethoxazole,[7] inhaled pentamidine,[6] or dapsone, with or without pyrimethamine, substantially reduces the incidence of *P. carinii* pneumonia.[8,9] Patients with a positive serum test for IgG antibodies to *Toxoplasma gondii* are also at risk for toxoplasmic encephalitis, the incidence of which is about 12 percent at one year among patients whose CD4 counts have fallen below 200 per cubic millimeter.[10] Trimethoprim–sulfamethoxazole and dapsone plus pyrimethamine prevent toxoplasmic encephalitis as well as *P. carinii* pneumonia.[9-11] Primary prophylaxis against both *P. carinii*

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*The members of the Swiss HIV Cohort Study are listed in the Appendix.

pneumonia and toxoplasmic encephalitis is an important component of the current treatment of patients with low CD4 counts.[12,13]

Combination antiretroviral therapy reduces levels of HIV RNA in plasma and increases CD4 counts in most patients within a few weeks.[14] It has also reduced the incidence of new opportunistic infections among patients with advanced HIV infection.[15,16] The function of the CD4 cells gained as a result of combination antiretroviral therapy is unclear, however. Several studies have found that the initial increase in CD4 cells during combination antiretroviral therapy is due predominantly to the clonal expansion of memory CD4 cells — a finding that raises the question of whether immunocompetence is truly restored.[17,18] Conversely, other groups have shown a normalization of cell-mediated immunity against opportunistic pathogens in functional tests within three to six months after the initiation of therapy.[19] In some patients, the T-cell repertoire may reach normal levels three to six months after combination antiretroviral therapy is begun.[20]

Whether the restoration of the immune response induced by combination antiretroviral therapy is sufficient to allow prophylaxis against *P. carinii* pneumonia to be discontinued remains unclear. Current guidelines state that the decision about whether to initiate or continue prophylaxis should be made on the basis of the lowest CD4 count ever measured in the patient (nadir count).[21] We prospectively studied the safety of discontinuing primary prophylaxis against *P. carinii* pneumonia in patients receiving combination antiretroviral therapy.

METHODS

The Swiss HIV Cohort Study

The Swiss HIV Cohort Study is a prospective cohort study with ongoing enrollment of HIV-infected persons 16 years of age or older. Enrollment in one of seven study centers (in Basel, Bern, Geneva, Lausanne, Lugano, St. Gallen, and Zurich) is independent of the disease stage and the degree of immunosuppression. Information is collected according to standardized criteria on structured forms at registration and at follow-up visits, which are scheduled at six-month intervals. The study design has been described in detail elsewhere.[22]

Inclusion and Exclusion Criteria

Patients receiving primary prophylaxis against *P. carinii* pneumonia and combination antiretroviral therapy, who had an increase in their CD4 count to 200 cells per cubic millimeter or higher and to at least 14 percent of total peripheral lymphocytes, and whose counts remained above these values for at least 12 weeks, were eligible for inclusion in our study. The local ethics committees of all seven study centers approved the study, and written informed consent was obtained from participants. The protocol stipulated that prophylaxis would be resumed if the CD4 count fell below at least one of the threshold values on two consecutive measurements. Recruitment started on June 28, 1997, and patients were followed prospectively within the framework of the Swiss HIV Cohort Study, except that CD4 counts were measured every three months. Study patients were instructed to contact the medical center if they had any symptoms suggestive of the presence of *P. carinii* pneumonia or toxoplasmic encephalitis.

End Points

A definite or presumptive diagnosis of *P. carinii* pneumonia was the primary study end point. A diagnosis was considered definite if *P. carinii* was found on microscopical analysis of induced sputum or bronchoalveolar fluid or on histologic examination of a lung specimen. A presumptive diagnosis was made if there was a history of dyspnea on exertion or nonproductive cough in the absence of evidence of bacterial pneumonia, if bronchoalveolar lavage was not performed, and if the patient responded to standard treatment for *P. carinii* pneumonia.

The secondary end point was toxoplasmic encephalitis. A definite diagnosis was made by histologic examination of brain-biopsy specimens. A presumptive diagnosis was made when the following were present: recent onset of a focal neurologic abnormality consistent with intracranial disease, a reduced level of consciousness, or headache; evidence on computed tomography or magnetic resonance imaging of at least one lesion with a mass effect or positive enhancement with contrast medium; and a response to standard treatment for toxoplasmic encephalitis.

Statistical Analysis

All participants with at least one follow-up evaluation were included in the analysis. The length of follow-up was measured from the date prophylaxis against *P. carinii* pneumonia was stopped. The closing date for the analysis was January 15, 1999. As of this date, all patients' charts were reviewed and patients were contacted by phone if the treating physician had not seen them within the previous month. If they could not be contacted, data were censored as of the date of the last follow-up visit. Events were assumed to have a Poisson distribution, and exact confidence intervals were calculated for the incidence of end points. All patients were considered to be at risk for *P. carinii* pneumonia, whereas only patients who were serologically positive for IgG antibodies to *T. gondii* were considered to be at risk for toxoplasmic encephalitis. We used Stata software (version 5.0, Stata, College Station, Tex.) for statistical analyses.

Historical Comparison Group

We examined the incidence of *P. carinii* pneumonia and toxoplasmic encephalitis in a historical comparison group of patients enrolled in the Swiss HIV Cohort Study from 1990 through 1994, before highly active antiretroviral therapy became widely available. We stratified patients according to their CD4 count at entry (<200, 200 to 500, or >500 cells per cubic millimeter); we then calculated the incidence of *P. carinii* pneumonia and toxoplasmic encephalitis in the first year after the date of enrollment. Patients in whom *P. carinii* pneumonia or toxoplasmic encephalitis was diagnosed within the first month after enrollment were excluded from the analysis, because in these patients, enrollment in the Swiss HIV Cohort Study was probably triggered by these events.

RESULTS

Characteristics of the Patients

A total of 396 patients fulfilled the entry criteria, according to the study data base. As of January 15, 1999, 279 (70.5 percent) of them had been enrolled. Seventeen (6.1 percent) were excluded from the present analysis, for the following reasons: 1 resumed prophylaxis because his CD4 count fell below the threshold value before the first follow-up visit, 1 resumed prophylaxis before the first follow-up visit after an episode of bacterial pneumonia, and 15 had not completed their first follow-up visit at the time the data were analyzed. This analysis therefore includes 262 (93.9 percent) of the 279 patients,

of whom 242 (92.4 percent) were followed until the closing date of January 15, 1999.

Data on 20 patients were censored before the closing date of the study, for the following reasons: 9 could not be reached by telephone, 2 died (1 had sudden death and 1 died of hepatocellular carcinoma); and 9 resumed prophylaxis because the CD4 count fell below the threshold value on a single measurement (4 patients) or two measurements (3 patients), because of recurrent episodes of respiratory tract infection that responded to aminopenicillin (1 patient), or for personal reasons (1 patient).

The characteristics of the study participants are shown in Table 1. The median age was 37 years, and two thirds of the patients were male. Sixty-three patients (24.0 percent) were in clinical stage C, according to the criteria of the Centers for Disease Control and Prevention (CDC),[23] and 113 (43.1 percent) had had a clinical condition known to be associated with an elevated risk of *P. carinii* pneumonia (recurrent thrush, candida esophagitis, weight loss, or fever).[5] One hundred twenty-one (46.2 percent) were positive for IgG antibodies to *T. gondii* and thus at risk for toxoplasmic encephalitis. The median CD4 count at study entry was 325 cells per cubic millimeter, and the median nadir (lowest-ever-measured) value was 110 cells per cubic millimeter (Fig. 1). Close to 90 percent of the patients were taking combination antiretroviral therapy that included at least one protease inhibitor. Only one patient with a history of disseminated *Mycobacterium avium* complex infection was receiving long-term macrolide therapy.

The 117 patients who fulfilled the entry criteria but were not enrolled and the 17 patients who were enrolled but were excluded from the analysis were similar to the 262 patients included in the analysis with regard to demographic variables; disease stage; nadir CD4 count; history of thrush, unexplained weight loss, or fever; and treatment history.

Incidence of Events during Follow-up

Data on incidence are summarized in Table 2. No diagnosis of *P. carinii* pneumonia or toxoplasmic encephalitis was recorded during follow-up. The incidence of each was therefore zero. The upper 99 percent Poisson confidence limits for the incidence were 1.93 per 100 patient-years for *P. carinii* pneumonia and 4.20 per 100 patient-years for toxoplasmic encephalitis. None of the patients had an AIDS-defining illness during follow-up. Four patients had an event that defines CDC stage B: one patient had oral candidiasis; one patient, thrombocytopenia; and two patients, cervical intraepithelial dysplasia.

Historical Comparison Group

Analyses of the historical comparison group were based on 3099 patients with a median age of 31 years, of whom 865 (27.9 percent) were female. The

TABLE 1. CHARACTERISTICS OF THE 262 STUDY PATIENTS AT BASE LINE AND CD4 COUNTS AND VIRAL LOAD AT THE END OF THE STUDY.

CHARACTERISTIC	VALUE
Age — yr	
Median	37
Range	25–80
Sex — no. (%)	
Male	177 (67.6)
Female	85 (32.4)
Risk category for transmission — no. (%)	
Men who had sex with men	96 (36.6)
Heterosexual sex	75 (28.6)
Injection-drug use	80 (30.5)
Other or unknown	11 (4.2)
Clinical stage — no. (%)*	
A	77 (29.4)
B	122 (46.6)
C	63 (24.0)
History of recurrent thrush, candida esophagitis, weight loss, or fever — no. (%)	113 (43.1)
Combination antiretroviral therapy — no. (%)	
Two drugs	35 (13.4)
Three or four drugs	227 (86.6)
Regimen including a protease inhibitor	232 (88.5)
IgG antibodies to *Toxoplasma gondii*	121 (46.2)
Prophylaxis against *Pneumocystis carinii* pneumonia — no. (%)	
Trimethoprim–sulfamethoxazole	224 (85.5)
Pentamidine	25 (9.5)
Dapsone and pyrimethamine	13 (5.0)
Duration of prophylaxis — mo	
Median	24.6
Range	3.3–100.3
Lowest CD4 count ever measured in patient†	
Cells/mm³	
Median	110
Range	0–240
Percentage of total peripheral lymphocytes	
Median	12
Range	0–31
Patients with lowest count <50/mm³ — no. (%)	57 (21.8)
CD4 count at study entry	
Cells/mm³	
Median	325
Range	210–806
Percentage of total peripheral lymphocytes	
Median	22
Range	14–55
CD4 count at end of study	
Cells/mm³	
Median	422
Range	122–1360
Percentage of total peripheral lymphocytes	
Median	25
Range	12–58
HIV RNA level at study entry — $\log_{10}$ copies/ml‡	
Median	2.0
Range	0.6–5.6
HIV RNA level at end of study — $\log_{10}$ copies/ml‡	
Median	1.9
Range	0.3–5.6

*The stages are those of the Centers for Disease Control and Prevention.[23]

†Lowest CD4 counts ever measured could be either above 200 per cubic millimeter or above 14 percent, since prophylaxis against *P. carinii* pneumonia was indicated if either of these two values was below the threshold.

‡HIV RNA was measured with either the standard Amplicor HIV-Monitor Test (Hoffmann–LaRoche, Basel, Switzerland) or a more sensitive modification of that test.[24] Values below the threshold were defined as 100 copies per milliliter with the standard test and equal to the limit of detection with the more sensitive modification (2 to 40 copies per milliliter).

Figure 1. CD4 Counts among Patients in Whom Prophylaxis against *Pneumocystis carinii* Pneumonia Was Stopped.

Shown are the lowest CD4 count ever measured in each patient, the count at study entry, and the count at the end of the study. The horizontal lines indicate the 25th, 50th, and 75th percentiles, and the I bars the 10th and 90th percentiles.

TABLE 2. FOLLOW-UP AND INCIDENCE OF *PNEUMOCYSTIS CARINII* PNEUMONIA AND TOXOPLASMIC ENCEPHALITIS AMONG 262 PATIENTS IN WHOM PROPHYLAXIS WAS DISCONTINUED.

VARIABLE	VALUE
***P. carinii* pneumonia**	
No. of patients at risk	262
Length of follow-up — mo	
Median	11.3
Range	3.0–18.8
Total follow-up — yr	238.2
Patients with ≥1 yr of follow-up — no. (%)	106 (40.5)
Incidence (per 100 patient-yr)	0
Upper 95% confidence limit*	1.26
Upper 99% confidence limit*	1.93
Toxoplasmic encephalitis	
No. of patients at risk	121
Length of follow-up — mo	
Median	11.0
Range	3.3–18.8
Total follow-up — yr	109.7
Patients with ≥1 yr of follow-up — no. (%)	49 (40.5)
Incidence (per 100 patient-yr)	0
Upper 95% confidence limit*	2.73
Upper 99% confidence limit*	4.20

*One-sided Poisson confidence limits are shown.

distribution according to risk factors for transmission was as follows: 1275 (41.1 percent) had a history of injection-drug use, 988 (31.9 percent) were men who had had sex with men, 756 (24.4 percent) were classified as having heterosexually acquired infection, and 80 (2.6 percent) had been infected through other or unknown routes. Calculations of incidence were based on 3099 patients and 2875 patient-years of follow-up for *P. carinii* pneumonia and 1089 patients with a positive IgG antibody test for *T. gondii* and 1004 patient-years of follow-up for toxoplasmic encephalitis. Data on incidence are shown in Table 3 according to the CD4 cell count at study entry.

DISCUSSION

We studied the incidence of *P. carinii* pneumonia and toxoplasmic encephalitis in patients in whom primary prophylaxis against *P. carinii* pneumonia was discontinued after their CD4 counts increased to at least 200 cells per cubic millimeter and 14 percent of the total lymphocyte count. We included the percentage of CD4 cells in addition to the absolute CD4 count in our criteria because the percentage of CD4 lymphocytes can be measured with greater reliability than the absolute number[25] and the value of 14 percent predicts an absolute count of 200 cells per cubic millimeter in a validated model.[26] CD4 counts were required to be above the defined threshold for at least 12 weeks before prophylaxis was stopped so as to achieve a reasonable margin of safety in determining that there had been a sustained increase. We could thus be confident that prophylaxis was being stopped only in patients with CD4 cell counts at levels that are known to confer protection against *P. carinii* pneumonia and toxoplasmosis in HIV-infected patients who are not treated with combination antiretroviral therapy.

In this population, the incidence of *P. carinii* pneumonia during the first year after prophylaxis was discontinued was zero, with an upper 99 percent confidence limit of less than 2 cases per 100 patient-years. The number of patients at risk for toxoplasmic encephalitis was lower, so that the estimate of the incidence of this condition is less precise, but the rate in the first year was almost certainly below 5 cases per 100 patient-years.

The estimated risk of *P. carinii* pneumonia or toxoplasmic encephalitis in our patients was similar to the risk among patients with CD4 counts below 200 cells per cubic millimeter who continue to take trimethoprim–sulfamethoxazole in the setting of a controlled clinical trial,[7] and it was smaller than the risk of *P. carinii* pneumonia in patients who receive inhaled pentamidine or dapsone, with or without pyrimethamine, in clinical trials.[6,9,10,27]

Our results suggest that combination antiretroviral therapy induces a clinically significant restoration

TABLE 3. INCIDENCE OF *PNEUMOCYSTIS CARINII* PNEUMONIA AND TOXOPLASMIC ENCEPHALITIS DURING THE FIRST YEAR AFTER STUDY ENTRY IN THE HISTORICAL COMPARISON GROUP OF 3099 PATIENTS, ACCORDING TO BASE-LINE CD4 COUNT.*

VARIABLE	CD4 COUNT AT STUDY ENTRY		
	<200 CELLS/mm³	200–500 CELLS/mm³	>500 CELLS/mm³
***Pneumocystis carinii* pneumonia**			
No. of patients at risk	918	1277	904
Median CD4 count (cells/mm³)	100	330	680
Incidence (per 100 patient-yr)	6.1	1.1	0.1
95% confidence interval	4.5–8.1	0.6–1.8	0.001–0.6
99% confidence interval	4.1–8.8	0.5–2.1	0.00001–0.8
Toxoplasmic encephalitis			
No. of patients at risk	363	437	289
Median CD4 count (cells/mm³)	100	326	670
Incidence (per 100 patient-yr)	15.9	1.2	0.4
95% confidence interval	11.7–21.0	0.4–2.8	0.001–2.0
99% confidence interval	10.6–22.7	0.3–3.4	0.001–2.6

*The historical comparison group was made up of patients enrolled in the Swiss HIV Cohort Study in 1990 through 1994.

of immunity against *P. carinii*. Our study subjects were at substantial risk for *P. carinii* pneumonia before the increase in their CD4 counts. Indeed, half of our patients had CD4 counts below 110 per cubic millimeter before they began combination antiretroviral therapy. This value is identical to the median CD4 count in a previous trial conducted within the framework of the Swiss HIV Cohort Study, in which the incidence of *P. carinii* pneumonia was 27 per 100 patient-years in the absence of combination antiretroviral therapy and of prophylaxis against *P. carinii* pneumonia.[6] Clearly, many cases of *P. carinii* pneumonia would have been expected in the present study population had immune reconstitution not been successful.

A historical comparison with patients whose CD4 cell counts never dropped below 200 cells per cubic millimeter and who were not treated with combination antiretroviral therapy provides further evidence of a genuine restoration of immune function in our study group. The median CD4 count at entry in our study was similar to the CD4 count among patients enrolled with CD4 counts of 200 to 500 cells per cubic millimeter during 1990 to 1994, before protease inhibitors became widely available. A comparison of estimates of incidence and confidence intervals for this historical group with the results of our present study group indicates that the estimates are similar.

Our results are in line with those of several ongoing studies that were recently presented in abstracts and preliminary reports.[28] Schneider and colleagues observed no events after primary or secondary prophylaxis was stopped, but their study was small and their data did not exclude the possibility of a substantial risk of *P. carinii* pneumonia.[29] We did not study the risk of stopping secondary prophylaxis. Interestingly, preliminary results are also encouraging in studies in which anticytomegalovirus treatment was stopped in patients with cytomegalovirus retinitis who had a good response to highly active antiretroviral therapy.[30,31] Stopping secondary prophylaxis against *P. carinii* pneumonia or toxoplasmic encephalitis may well be safe in such patients, but further data are needed before this approach can be recommended.

The median follow-up in this study was more than 11 months, and more than 100 patients were followed for at least 1 year. However, our study cannot exclude with certainty the possibility of an increase in the risk of *P. carinii* pneumonia and toxoplasmic encephalitis one year after prophylaxis stopped. Immune function increases with time after the successful initiation of combination antiretroviral therapy.[17] Moreover, the incidence of opportunistic infections remains high during the first months of treatment but declines thereafter.[32] An increase in the risk of *P. carinii* pneumonia is therefore unlikely if CD4 counts are maintained at safe levels. If the failure of therapy leads to a decline in CD4 counts to levels below 200 cells per cubic millimeter, therefore, prophylaxis should be reintroduced. We restarted prophylaxis for this reason in only seven patients.

This was an uncontrolled, observational study. The possibility of bias due to the selection of patients at low risk must be considered, but such bias is unlikely. The Swiss HIV Cohort Study includes about 70 percent of all patients with advanced disease in the country.[33] A large proportion of the eligible patients were included in our analysis, and those who were not included had characteristics similar to those of the study patients. We considered performing a randomized, controlled trial but concluded that it would not be possible to recruit the large number of patients required to show equivalence between the group in which prophylaxis was stopped and that in which it was continued.

In conclusion, we have shown that it is safe to stop primary prophylaxis against *P. carinii* pneumonia in patients who have responded to combination antiretroviral therapy with an increase in the CD4 count to at least 200 cells per cubic millimeter and 14 percent of total peripheral lymphocytes that has been sustained for at least 12 weeks. The study participants in this large community-based cohort included men and women at all clinical stages of HIV disease, who had acquired HIV infection through both sexual and parenteral routes. The results should therefore be applicable to patients seen in daily clinical practice, if our entry and follow-up criteria are followed.

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APPENDIX

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REFERENCES

1. Update: acquired immunodeficiency syndrome — United States. MMWR Morb Mortal Wkly Rep 1986;35:757-60, 765-6.
2. Hoover DR, Saah AJ, Bacellar H, et al. Clinical manifestations of AIDS in the era of pneumocystis prophylaxis. N Engl J Med 1993;329:1922-6.
3. Harris JE. Improved short-term survival of AIDS patients initially diagnosed with *Pneumocystis carinii* pneumonia, 1984 through 1987. JAMA 1990;263:397-401.
4. Chaisson RE, Gallant JE, Keruly JC, Moore RD. Impact of opportunistic disease on survival in patients with HIV infection. AIDS 1998;12:29-33.
5. Phair J, Muñoz A, Detels R, et al. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. N Engl J Med 1990;322:161-5.
6. Hirschel B, Lazzarin A, Chopard P, et al. A controlled study of inhaled pentamidine for primary prevention of *Pneumocystis carinii* pneumonia. N Engl J Med 1991;324:1079-83.
7. Schneider MME, Hoepelman AIM, Eeftinck Schattenkerk JKM, 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.
8. Bozzette SA, Finkelstein DM, Spector SA, 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.
9. Bucher HC, Griffith L, Guyatt GH, Opravil M. Meta-analysis of prophylactic treatments against *Pneumocystis carinii* pneumonia and toxoplasma encephalitis in HIV-infected patients. J Acquir Immune Defic Syndr Hum Retrovirol 1997;15:104-14.
10. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. Clin Infect Dis 1995; 20:531-41.
11. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. Ann Intern Med 1992;17:106-11.
12. Recommendations for prophylaxis against *Pneumocystis carinii* pneumonia for adults and adolescents infected with human immunodeficiency virus. MMWR Morb Mortal Wkly Rep 1992;41(RR-4):1-11.
13. Masur H. Prevention and treatment of pneumocystis pneumonia. N Engl J Med 1992;327:1853-60. [Erratum, N Engl J Med 1993;328: 1136.]
14. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med 1997;337:734-9.
15. Egger M, Hirschel B, Francioli P, et al. Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. BMJ 1997;315:1194-9.
16. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338:853-60.
17. Pakker NG, Notermans DW, de Boer RJ, 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.
18. Connors M, Kovacs JA, Krevat S, et al. HIV infection induces changes in CD4+ T-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.
19. Li TS, Tubiana R, Katlama C, Calvez V, Ait Mohand H, Autran B. Long-lasting recovery in CD4 T-cell function and viral load reduction after highly active antiretroviral therapy in advanced HIV-1 disease. Lancet 1998;351:1682-6.
20. Gorochov G, Neumann AU, 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.
21. USPHS/IDSA Prevention of Opportunistic Infections Working Group. Preface to the 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Clin Infect Dis 1997;25:Suppl 3:S299-S312.
22. Ledergerber B, von Overbeck J, Egger M, Lüthy R. The Swiss HIV Cohort Study: rationale, organization and selected baseline characteristics. Soz Praventivmed 1994;39:387-94.
23. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mortal Wkly Rep 1992;41(RR-17):1-19.
24. Schockmel GA, Yerly S, Perrin L. Detection of low HIV-1 RNA levels in plasma. J Acquir Immune Defic Syndr Hum Retrovirol 1997;14:179-83.
25. Taylor JM, Fahey JL, Detels R, Giorgi JV. CD4 percentage, CD4 number, and CD4:CD8 ratio in HIV infection: which to choose and how to use. J Acquir Immune Defic Syndr 1989;2:114-24.
26. Kidd PG, Cheng SC, Paxton H, Landay A, Gelman R. Prediction of CD4 count from CD4 percentage: experience from three laboratories. AIDS 1993;7:933-40.
27. Torres RA, Barr M, Thorn M, et al. Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of Pneumocystis carinii pneumonia and toxoplasmic encephalitis. Am J Med 1993;95:573-83.
28. Currier JS. OI prophylaxis in antiretroviral responders: stay the course or bite the bullet? AIDS Clin Care 1998;10:73-5, 79-80.
29. Schneider MME, Borleffs JCC, Stolk RP, Jaspers CA, Hoepelman AIM. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. Lancet 1999;353:201-3.
30. 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.
31. Macdonald JC, Torriani FJ, Morse LS, Karavellas MP, Reed JB, Freeman WR. 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.
32. Michelet C, Arvieux C, François C, et al. Opportunisitc infections occurring during highly active antiretroviral treatment. AIDS 1998;12:1815-22.
33. Gebhardt M, Rickenbach M, Egger M, Swiss HIV Cohort Study. Impact of antiretroviral combination therapies on AIDS surveillance reports in Switzerland. AIDS 1998;12:1195-201.