Long-term safety of discontinuation of secondary prophylaxis against Pneumocystis pneumonia: Prospective multicentre study

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Objectives: To assess the long-term safety of discontinuation of secondary anti-*Pneumocystis* prophylaxis in HIV-infected adults treated with antiretroviral combination therapy and who have a sustained increase in CD4 cell counts.

Design: Prospective observational multicentre study.

Patients and methods: The incidence of *P. jirovecii* pneumonia after discontinuation of secondary prophylaxis was studied in 78 HIV-infected patients on antiretroviral combination therapy after they experienced a sustained increase in CD4 cell counts to at least 200×10^6 cells/l and 14% of total lymphocytes measured twice at least 12 weeks apart.

Results: Secondary prophylaxis was discontinued at a median CD4 cell count of 380×10^6 cells/l. The median follow-up period after discontinuation of secondary prophylaxis was 40.2 months, yielding a total of 235 person-years of follow-up. No cases of recurrent *P. jirovecii* pneumonia occurred during this period. The incidence was thus 0 per 100 person-years with a 95% upper of confidence limit of 1.3 cases per 100 patient-years.

Conclusions: Discontinuation of secondary prophylaxis against *P. jirovecii* pneumonia is safe even in the long term in patients who have a sustained immunologic response on antiretroviral combination therapy.

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Keywords: HIV, CD4 cell count, plasma HIV RNA, antiretroviral combination therapy, *Pneumocystis jirovecii* pneumonia, primary prophylaxis, secondary prophylaxis, discontinuation of prophylaxis, immune reconstitution, cohort study

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Introduction

Potent antiretroviral treatment has lead to a dramatic decrease in HIV-associated morbidity and mortality [1,2]. This decline is the result of a successful suppression of plasma virus concentration which leads to an increase in CD4-positive T cell lymphocytes associated with a clinically important restoration of the immune response and protection against opportunistic infections.

The question as to whether or not treatment-associated restoration of the immune response allows primary and secondary prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) to be discontinued has been examined in combined cohort studies and prospective trials. While there are convincing and long-term results with regard to the safety of discontinuation of primary prophylaxis in patients who responded to potent antiretroviral therapy with a sustained increase in CD4 cell counts [3–11], results from two randomized controlled trials [12,13] and results from several cohort studies [4,6,7,14,15] indicate that the discontinuation of maintenance therapy is also safe [16]. However, except for the recently published randomized controlled trial by Mussini *et al.* [13] median follow-up time in these studies was less than 18 months (see Table 3) and some concern about the long-term safety of stopping secondary prophylaxis therefore remains. Thus, the decision to discontinue a convenient, highly effective, and inexpensive prophylaxis such as thrice weekly trimethoprim–sulfamethoxazole asks for a higher level of evidence and certainty.

We therefore conducted this prospective multicentre study to evaluate the long-term safety of discontinuing chemoprophylaxis against recurrent PCP in patients whose CD4 cell count had risen to $> 200 \times 10^6$/l and 14% of peripheral lymphocyte count for at least 12 weeks during an median observational period of more than 3 years.

Patients and methods

The Swiss HIV Cohort Study

Participants of the Swiss HIV Cohort Study could be included into the study. The Swiss HIV Cohort Study (SHCS; www.shcs.ch) is a prospective cohort study with ongoing enrolment of adult HIV-infected patients [17,18]. Patients are followed in one of seven study centres (Basle, Berne, Geneva, Lausanne, Lugano, St Gall, and Zurich). Enrolment is independent of stage of disease or degree of immunosuppression, and information is collected according to standardized criteria on structured forms at enrolment and at follow-up visits at 6-month intervals. Written informed consent is mandatory for inclusion into the study and the study is approved by all local ethical committees. Clinical stage is defined according to the 1993 classification system for HIV infection of the Centers for Disease Control and Prevention (CDC) [19]. CD4 cell counts are measured using flow-cytometric assays and plasma HIV-RNA levels are measured using the Roche Amplicor assay (Roche Diagnostics, Basle, Switzerland) with a lower detection limit of about 200 copies/ml. An ultrasensitive modification of the assay with a limit of detection of 2–40 copies/ml was introduced during 1998 [20].

Inclusion and exclusion criteria

SHCS participants receiving secondary prophylaxis after a definitive or presumed diagnosis of PCP were eligible if they had a response to combination antiretroviral therapy consisting of at least two drugs with a sustained increase of the CD4 cell counts to at least 200×10^6/l and 14% of the peripheral lymphocyte count for at least 12 weeks.

Patients who took chronically immunosuppressive drugs (except hydroxyurea) in a maximal dosage of 500 mg twice daily, or had a history of toxoplasmic encephalitis were excluded.

According to the protocol secondary PCP prophylaxis would be resumed if: (i) the CD4 cell count fell below one of the threshold values on two consecutive measurements; or (ii) in the case of newly prescribed immunosuppressive drugs; or (iii) according to the patient's or the physician's wish. Recruitment started in January 1999, and ended in September 2002, follow-up was censored in September 2003.

End points

A definitive or presumed diagnosis of PCP was the primary endpoint of this study: A definitive diagnosis of PCP was defined as microscopic detection of *P. jirovecii* in spontaneous or induced sputum or bronchoalveolar fluid, or on histologic examination of a lung specimen. A presumed diagnosis of PCP was defined as the presence of dyspnea on exertion, or a non-productive cough without evidence of bacterial pneumonia in a patient who responded to standard PCP treatment.

The secondary end points of the study were a definitive or presumed diagnosis of toxoplasmic encephalitis or death.

Statistical analysis

The closing date for the present analysis was 17 September 2003. Follow-up time was the time from entry into the study until the patient was last seen by the treating physician. Information about epidemio-

logical characteristics and clinical history were taken from the SHCS database.

Events were assumed to have a Poisson distribution, and exact 95% confidence intervals were calculated for the incidence of endpoints. One-sided upper 95% confidence limits were calculated if no event was recorded. We used Stata software (version 8.0, College Station, Texas, USA) for statistical analysis.

Results

A total of 274 patients followed up within the SHCS fulfilled the entry criteria. As of September 2002, 78 (28.5%) of them had consented to be enrolled. The enrolled patients did not differ significantly from the unenrolled patients with regard to CD4 cell count, CD4 cell percentage, plasma HIV RNA, age or presumed mode of HIV transmission. Their baseline characteristics at the time of the discontinuation of secondary prophylaxis against PCP are shown in Table 1.

Most of the patients were men (74%), the median age was 39 years. Fifty-three (68%) of the enrolled patients had plasma HIV RNA levels < 50 copies/ml, and the median CD4 cell count was 380×10^6/l at the time secondary prophylaxis was discontinued. The median nadir CD4 cell count had been 24×10^6/l (5% of total peripheral lymphocytes). In 61 patients (78%) the discontinued prophylactic regimen consisted of trimethoprim–sulfamethoxazole, 11 patients (14%) stopped aerosolised pentamidine and in the remaining six patients (8%) the secondary prophylaxis consisted of dapsone, dapsone/pyrimethamine, atovaquone or other drugs. Two of the enrolled patients had a history of one relapse and one of two relapses of PCP.

The median duration of the secondary prophylaxis after PCP was 40 months. All enrolled patients had to be on antiretroviral treatment. The median time since initiating antiretroviral therapy was 35 months (interquartile range, 26–40 months). In 97% the antiretroviral therapy consisted of at least three drugs, while 28% were treated with at least one protease inhibitor; only two patients were on a two-drug regimen.

Table 1. Characteristics of 78 patients who discontinued secondary prophylaxis.

Characteristics	Study participants (n = 78)
Age (years) [median (IQR)]	39 (36–46)
Sex [n (%)]	
Male	58 (74)
Female	20 (26)
Risk factor for transmission [n (%)]	
Men who have sex with men	33 (42)
Heterosexual contact	31 (40)
Injecting drug use	9 (12)
Unknown or other	5 (6)
CD4 cell count during *P. jirovecii* pneumonia ($\times 10^6$/l) [median (IQR)]	41 (17–87)
Percentage of total peripheral lymphocytes [median (IQR)]	6 (2–10)
CD4 cell count at discontinuation of secondary prophylaxis ($\times 10^6$/l) [median (IQR)]	380 (310–533)
Percentage of total peripheral lymphocytes [median (IQR)]	22 (18–28)
CD4 count at end of study ($\times 10^6$/l) [median (IQR)]	463 (343–600)
Percentage of total peripheral lymphocytes [median (IQR)]	26 (20–31)
Plasma HIV-1 RNA level at discontinuation of secondary prophylaxis (copies/ml) [median (IQR)]	< 50 (< 50–80)
Patients with plasma HIV-1 RNA below 50 copies/ml at discontinuation [n (%)]	53 (68)
Plasma HIV-1 RNA level at end of study (copies/ml) [median (IQR)]	< 50 (< 50–< 50)
Patients with plasma HIV-1 RNA < 50 copies/ml at end of study [n (%)]	59 (76)
Duration of prophylaxis since *P. jirovecii* pneumonia at study entry (months) [median (IQR)]	40 (28–54)
Prophylaxis against *P. jirovecii* pneumonia at study entry [n (%)]	
Trimethoprim–sulfamethoxazole	61 (78)
Aerosolized pentamidine	11 (14)
Dapsone	1 (1)
Dapsone/pyrimethamine	1 (1)
Atovaquone	1 (1)
Other	3 (4)
Duration of highly active antiretroviral therapy[a] at discontinuation of secondary prophylaxis (months) [median (IQR)]	35 (26–40)
Highly active antiretroviral therapy[a] [n (%)]	
Three drugs	54 (69)
More than three drugs	22 (28)
Regimen including one or more protease inhibitors	67 (86)
Regimen including one non-nucleoside reverse transcriptase inhibitor	10 (13)

[a]Two patients were treated with two drugs only. IQR, Interquartile range.

Seven patients were withdrawn from the study because their chemoprophylaxis against PCP had to be re-initiated. In three of them the reason for restarting the secondary prophylaxis was a decrease of the CD4 cell count to $< 200 \times 10^6$/l or $< 14\%$ of total peripheral lymphocytes documented by two consecutive measurements; in two patients the treating physician decided to restart prophylaxis because of a decrease of the CD4 cell count but without confirmation in a second measurement; in one patient the prophylaxis was re-initiated according to the patient's wish; and in one patient the reason for re-starting the trimethoprim–sulfamethoxazole were recurrent episodes of sinusitis. Two patients were lost to follow-up, one because he moved outside of Switzerland and the other because he withdrew from the study.

Incidence of PCP

During a total follow-up time of 235 person-years there were no cases of PCP, corresponding to a 95% upper confidence limit of 1.3 per 100 person-years (Table 2). There was no diagnosis of toxoplasmic encephalitis and no deaths during the study.

Discussion

The discontinuation of secondary prophylaxis against PCP in HIV infected patients with a sustained increase in the CD4 cell count to $> 200 \times 10^6$/l and 14% of total peripheral lymphocytes could significantly improve the patients' quality of life. However, from the era before potent antiretroviral therapy became available it is known that the incidence of a PCP relapse after an initial episode is up to 50% within 6 months without prophylaxis compared to 3.5–18% with secondary prophylaxis [21,22]. In addition, there is uncertainty about continued risk of PCP recurrence despite quantitative increases of the CD4 cell counts in the long term. Thus, the potential benefits of a discontinuation of the secondary prophylaxis have to be balanced against the remaining risk for a PCP relapse and against the potential problems associated with the prophylactic drug such as hypersensitivity to sulfonamides [23–25], development of drug-resistant *P. jirovecii* [26,27] and bacteria [28] and costs.

Our study supports the hypothesis that a sustained increase in the CD4 cell count to $> 200 \times 10^6$/l and 14% of the total peripheral lymphocyte count over at least 12 weeks, leads to a significant immune restoration with protection against opportunistic infections over a median follow-up of 3.3 years. When the study was designed the required increase of the CD4 cell count over at least 12 weeks took into account the then published presumed minimal time required for naive CD4 cells to recover [29,30]. None of the 78 prospectively enrolled patients developed a PCP after secondary prophylaxis was discontinued. It is noteworthy that the follow-up time in this study was 235 person-years, the longest follow-up time described so far. The upper 95% confidence limit of the incidence of PCP relapse was only 1.3 cases per 100 person-years of follow-up. Although the possibility of a PCP relapse cannot be excluded absolutely, the remaining risk seems to be very low. In addition, no case of toxoplasmic encephalitis has occurred. Thus, these results indicate that discontinuation of secondary prophylaxis is safe over an extended observation period in patients who respond to antiretroviral therapy with a sustained increase in the CD4 cell count to $> 200 \times 10^6$/l and 14% of the total lymphocyte count, irrespective of the CD4 cell nadir.

Several studies have previously addressed this issue with similar results (Table 3), but their main limitations were short periods of observation, small sample sizes and therefore wide confidence intervals of the point estimates of low incidence rates observed. In contrast to the previously published studies showing relapse rates of zero after discontinuation of secondary PCP prophylaxis a recent randomized controlled trial by Mussini *et al.* described one definitive and one presumptive case of PCP in patients who discontinued maintenance therapy [13]. These relapses occurred in patients with undetectable plasma HIV RNA and CD4 cell counts $> 200 \times 10^6$/l but one of these patients had received corticosteroids for asthma. Cases of PCP despite high CD4 cell counts were also, albeit rarely, observed in patients who discontinued primary prophylaxis [31]. The CD4 cell count during antiretroviral therapy remains a very good, but not an absolutely perfect, marker of immunocompetence against opportunistic infections [32] and awareness of clinicians caring for

Table 2. Incidence of *Pneumocystis jirovecii* pneumonia (PCP).

No at risk	Median follow-up time [years (range)]	Total follow-up time (years)	Events (n)	Incidence of PCP per 100 patient-years (95% CI)
78	3.3 (2.8–3.5)	235	0	0 (0–1.3)

Table 3. Overview of published studies with at least 20 patients included investigating the safety of stopping secondary prophylaxis against *Pneumocystis jirovecii* pneumonia.

Study (location, year of publication)	Study type	Inclusion criteria	Patients (n)	Median follow-up (months)	Person-years of follow-up	No of cases of *P. jirovecii*	Incidence per 100 person-years (95% CI)
Lopez *et al.* [12] (Spain 2001)	RCT	CD4 cells $\geq 200 \times 10^6$/l and plasma HIV RNA < 5000/ml for at least 3 months	60	12	65.0	0	0 (0–4.57)
Kirk *et al.* [6] (Denmark 1999)	POS	CD4 cells > 200×10^6/l for at least 6 months	26	9.6	20.0	0	0 (0–18.4)
Koletar *et al.* [7] (USA 2001)	POS	CD4 cells $\geq 200 \times 10^6$/l for at least 3 months	129	14.5	153	0	0 (0–1.96)
Ledergerber *et al.* [14] (Europe 2001)	RCS	CD4 cells > 200×10^6/l	325	13	374	0	0 (0–0.8)
Mussini *et al.* [13] (Italy 2003)	RCT	CD4 cells > 200×10^6/l for at least 1 month and on highly active antiretroviral therapy	77	27.4	166.7	2	1.2 (0.1–4.3)
Abgrall *et al.* [15] (France 2001)	RCS	CD4 cells > 200×10^6/l and on highly active antiretroviral therapy	51	8.5	37	0	0 (0–7.84)
Soriano *et al.* [41] (Spain 2000)	RCS	CD4 cells > 100×10^6/l and plasma HIV RNA < 500/ml after 3 months of highly active antiretroviral therapy	29	18	76.5	1[a]	1.3 (0–7.2)
Weverling *et al.* [4] (Europe/Israel 1999)	RCS	Start of highly active antiretroviral therapy	59	5	50	0	0 (0–7.4)
Current study (Switzerland 2004)	POS	CD4 cells > 200×10^6/l and 14% for at least 12 weeks and on highly active antiretroviral therapy of at least two drugs	78	39.6	235	0	0 (0–1.3)

[a]One patient developed a *Pneumocystis jirovecii* pneumonia after interrupted antiretroviral treatment for 6 weeks because of gastrointestinal intolerance at a CD4 cell count of 46×10^6/l and a plasma HIV RNA of > 500 000/ml. CI, Confidence interval; RCT, randomized controlled trial; POS, prospective observational study; RCS, retrospective analysis within cohort studies.

HIV-infected patients who discontinue prophylaxis is vital. We agree with Mussini *et al.* who point out that the dynamics of the CD4 cell count have to be monitored closely and that a re-initiation of secondary prophylaxis should be considered in the case of additional risk factors, such as glucocorticoid treatment or antineoplastic chemotherapy.

A particular issue of discontinuation trimethoprim–sulfamethoxazole is the loss of a potential secondary benefit, namely the protection against cerebral toxoplasmosis and common bacterial infections [22,33,34]. There was no case of toxoplasmic encephalitis in our study population as was to be expected given the shown safety of discontinuation of primary prophylaxis against toxoplasmosis [35].

Prior to the introduction of highly active antiretroviral therapy (HAART) Hirschtick *et al.* were the first to report a significant reduction in the incidence of bacterial pneumonia (67%) among HIV-infected patients receiving prophylaxis with trimethoprim–sulfamethoxazole [36]. However, since the introduction of HAART the incidence of bacterial pneumonia has significantly decreased [37,38]. Recently published data of discontinuation primary and secondary PCP prophylaxis did not provide evidence of a significantly increased risk of bacterial pneumonia among patients who have discontinued the prophylaxis [7,12,31,39].

This observation was confirmed by a prospective cohort study in which the incidence of community-acquired pneumonia was compared between 336 patients with a sustained CD4 cell count increase to $\geq 200 \times 10^6$/l and 14% of the total lymphocyte count who discontinued trimethoprim–sulfamethoxazole prophylaxis, and 78 patients who continued receiving prophylaxis [40]. The difference in the incidence rate was not statistically significant and event rates were very low. Thus, this analysis showed that discontinuation of trimethoprim–sulfamethoxazole prophylaxis is not associated with a clinically significant increase in the incidence of bacterial pneumonia.

In our study we did not routinely check for the incidence of bacterial infections, but there was one patient who was withdrawn from the study because he restarted trimethoprim–sulfamethoxazole because of recurrent sinusitis.

In conclusion, the present study adds to the evidence that discontinuation of secondary prophylaxis against PCP in patients who have a sustained immunological response to antiretroviral combination therapy indicated by a CD4 cell count $> 200 \times 10^6$/l and 14% of the total lymphocyte count is safe with a minimal risk of recurrent PCP even in the long term.

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References

1. Egger M, Hirschel B, Francioli P, Sudre P, Wirz M, Flepp M, *et al.* **Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study.** *BMJ* 1997, **315**:1194–1199.
2. Palella FJ, Delaney KM, Moorman AC, Loveless AO, Fuhrer J, Satten GA, *et al.* **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection.** *N Engl J Med* 1998, **338**:853–860.
3. Furrer H, Egger M, Opravil M, Bernasconi E, Hirschel B, Battegay 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**:1301–1306.
4. Weverling GJ, Mocroft A, Ledergerber B, Kirk O, Gonzalez-Lahoz J, d'Arminio Monforte A, *et al.* **Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. EuroSIDA Study Group.** *Lancet* 1999, **353**:1293–1298.
5. Schneider MME, Borleffs JCC, Stolk RP, Jaspers AJJ, Hoepelman AIM. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet* 1999, **353**:201–203.
6. Kirk O, Lundgren JD, 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**:1647–1651.
7. Koletar SL, Heald AE, Finkelstein D, Hafner R, Currier JS, McCutchan JA, *et al.* **A prospective study of discontinuing primary and secondary *Pneumocystis carinii* pneumonia prophylaxis after CD4 cell count increase to > 200 × 10^6/l.** *AIDS* **2001, 15:1509–1515.**
8. Garcia VE, de Gorgolas HM, Garcia DR, Fernandez Guerrero ML. Withdrawal of *Pneumocystis carinii* pneumonia prophylaxis in patients receiving efficacious combined antiretroviral treatment. Study of 85 cases (in Spanish). *Med Clin (Barc)* 1999, **113**:89–90.
9. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. **Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds.** *J Infect Dis* 2000, **182**:611–615.
10. Yangco BG, Von Bargen JC, Moorman AC, Holmberg SD. **Discontinuation of chemoprophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection. HIV Outpatient Study (HOPS) Investigators.** *Ann Intern Med* 2000, **132**: 201–205.
11. Jubault V, Pacanowski J, Rabian C, Viard JP. **Interruption of prophylaxis for major opportunistic infections in HIV- infected patients receiving triple combination antiretroviral therapy.** *Ann Med Interne (Paris)* 2000, **151**:163–168.
12. Lopez Bernaldo de Quiros JC, Miro JM, Pena JM, Podzamczer D, Alberdi JC, Martinez E, *et al.* **A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98.** *N Engl J Med* 2001, **344**:159–167.
13. Mussini C, Pezzotti P, Antinori A, Borghi V, Monforte A, Govoni A, *et al.* **Discontinuation of secondary prophylaxis for *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients: a randomized trial by the CIOP Study Group.** *Clin Infect Dis* 2003, **36**:645–651.
14. Ledergerber B, Mocroft A, Reiss P, Furrer H, Kirk O, Bickel M, *et al.* **Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups.** *N Engl J Med* 2001, **344**:168–174.
15. Abgrall S, Matheron S, Le M, V, Dupont C, Costagliola D. ***Pneumocystis carinii* pneumonia recurrence in HIV patients on highly active antiretroviral therapy: secondary prophylaxis.** *J Acquir Immune Defic Syndr* 2001, **26**:151–158.
16. Kaplan JE, Masur H, Holmes KK. **Guidelines for preventing opportunistic infections among HIV-infected persons–2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America.** *MMWR Morb Mortal Wkly Rep* 2002, **51**:1–52.
17. Ledergerber B, von Overbeck J, Egger M, Lüthy R. **The Swiss HIV cohort study: rationale, organization and selected baseline characteristics.** *Soz Präventivmed* 1994, **39**:387–394.
18. Sudre P, Rickenbach M, Taffé P, Janin P, Volkart AC, Francioli P, *et al.* **Clinical epidemiology and research on HIV infection in Switzerland: the Swiss HIV Cohort Study 1988-2000.** *Schweiz Med Wochenschr* 2000, **130**:1493–1500.
19. Centers for disease control. **1993 Classification system for HIV infection and expanded surveillance case definition for acquired immunodeficiency syndrome (AIDS) among adolescents and adults.** *MMWR Morb Mortal Wkly Rep* 1992, **41**(RR-17):1–19.
20. Schockmel GA, Yerly S, Perrin L. **Detection of low HIV-1 RNA levels in plasma.** *J Acquir Immune Defic Syndr Hum Retrovirol* 1997, **14**:179–183.
21. Centers for disease control. **Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus.** *MMWR Morb Mortal Wkly Rep* 1989, **38**(S-5):1–9.
22. Hardy WD, Feinberg J, Finkelstein DM, Power ME, He W, Kaczka C, *et al.* **A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trials Group Protocol 021.** *N Engl J Med* 1992, **327**:1842–1848.
23. Jung AC, Paauw DS. **Management of adverse reactions to trimethoprim-sulfamethoxazole in human immunodeficiency virus-infected patients.** *Arch Intern Med* 1994, **154**:2402–2406.
24. Masur H. **Prevention and treatment of *Pneumocystis* pneumonia.** *N Engl J Med* 1992, **327**:1853-1860.
25. Bozzette SA, Finkelstein DM, Spector SA, Frame P, Powderly WG, He W, *et al.* **A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group.** *N Engl J Med* 1995, **332**:693–699.
26. Helweg-Larsen J, Benfield TL, Eugen-Olsen J, Lundgren JD, Lundgren B. **Effects of mutations in *Pneumocystis carinii* dihydropteroate synthase gene on outcome of AIDS-associated *P. carinii* pneumonia.** *Lancet* 1999, **354**:1347–1351.
27. Nahimana A, Rabodonirina M, Helweg-Larsen J, Meneau I, Francioli P, Bille J, *et al.* **Sulfa resistance and dihydropteroate synthase mutants in recurrent *Pneumocystis carinii* pneumonia.** *Emerg Infect Dis* 2003, **9**:864–867.
28. Martin JN, Rose DA, Hadley WK, Perdreau-Remington F, Lam PK, Gerberding JL. **Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS era.** *J Infect Dis* 1999, **180**:1809–1818.
29. 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**:1682–1686.
30. Lederman MM, Connick E, Landay A, Kuritzkes DR, Spritzler J, St Clair M, *et al.* **Immunologic responses associated with 12 weeks of combination antiretroviral therapy consisting of zidovudine, lamivudine, and ritonavir: results of AIDS Clinical Trials Group Protocol 315.** *J Infect Dis* 1998, **178**:70–79.
31. Furrer H, Opravil M, Rossi M, Bernasconi E, Telenti A, Bucher H, *et al.* **Discontinuation of primary prophylaxis in HIV-infected patients at high risk of *Pneumocystis carinii* pneumonia: prospective multicentre study.** *AIDS* 2001, **15**:501–507.

32. Ledergerber B, Egger M, Erard V, Weber R, Hirschel B, Furrer H, *et al.* **AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study.** *JAMA* 1999, **282**:2220–2226.
33. Carr A, Tindall B, Brew BJ, Marriott DJ, Harkness JL, Penny R, *et al.* **Low-dose trimethoprim-sulfomethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS.** *Ann Intern Med* 1992, **117**:106–111.
34. Podzamczer D, Salazar A, Jimenez J, Consiglio E, Santin M, Casanova A, *et al.* **Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of *Pneumocystis pneumonia* and toxoplasmosis in patients infected with HIV.** *Ann Intern Med* 1995, **122**:755–761.
35. 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, **335**:2217–2218.
36. Hirschtick RE, Glassroth J, Jordan MC, Wilcosky TC, Wallace JM, Kvale PA, *et al.* **Bacterial pneumonia in persons infected with the human immunodeficiency virus.** *N Engl J Med* 1995, **333**:845–841.
37. Sullivan JH, Moore RD, Keruly JC, Chaisson RE. **Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection.** *Am J Respir Crit Care Med* 2000, **162**:64–67.
38. de Gaetano DK, Bertagnolio S, Tumbarello M, Tacconelli E, Cataldo M, Longo B, *et al.* **Effect of highly active antiretroviral therapy on the incidence of bacterial pneumonia in HIV-infected subjects.** *Int J Antimicrob Agents* 2000, **16**:357–360.
39. Mussini C, Pezzotti P, Govoni A, Borghi V, Antinori A, d'Arminio MA, *et al.* **Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study.** *J Infect Dis* 2000, **181**: 1635–1642.
40. Eigenmann C, Flepp M, Bernasconi E, Schiffer V, Telenti A, Bucher H, *et al.* **Low incidence of community-acquired pneumonia among human immunodeficiency virus-infected patients after interruption of *Pneumocystis carinii* pneumonia prophylaxis.** *Clin Infect Dis* 2003, **36**:917–921.
41. Soriano V, Dona C, Rodriguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. **Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy.** *AIDS* 2000, **14**:383–386.

Appendix

Members of the Swiss HIV Cohort Study

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