Peer reviewed article

# Disseminated *M. avium* Complex infection in the Swiss HIV Cohort Study: Declining incidence, improved prognosis and discontinuation of maintenance therapy[1]

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## Summary

*Background:* Introduction of potent antiretroviral combination therapy (ART) has reduced overall morbidity and mortality amongst HIV-infected adults. Some prophylactic regimes against opportunistic infections can be discontinued in patients under successful ART.

*Questions under study:* (1) The influence of the availability of ART on incidence and mortality of disseminated *M. avium* Complex infection (MAC). (2) The safety of discontinuation of maintenance therapy against MAC in patients on ART.

*Setting:* The Swiss HIV-Cohort Study, a prospective multicentre study of HIV-infected adults.

*Methods:* Patients with a nadir CD4 count below 50 cells/mm$^3$ were considered at risk for MAC and contributed to total follow-up time for calculating the incidence. Survival analysis was performed by using Kaplan Meier and Cox proportional hazards methods. Safety of discontinuation of maintenance therapy was evaluated by review of the medical notes.

*Results:* 398 patients were diagnosed with MAC from 1990 to 1999. 350 had a previous CD4 count below 50 cells/mm$^3$. A total of 3208 patients had a nadir CD4 count of less than 50 cells/mm$^3$ during the study period and contributed to a total follow-up of 6004 person-years. The incidence over the whole study period was 5.8 events per 100 person-years. In the time period of available ART the incidence of MAC was significantly reduced (1.4 versus 8.8 events per 100 person-years, p <0.001). Being diagnosed after 1995 was the most powerful predictor of better survival (adjusted hazard ratio for death: 0.27; p <0.001). None of 24 patients discontinuing maintenance therapy while on ART experienced recurrence of MAC during a total follow-up of 56.6 person-years (upper 95% confidence limit 5.3 per 100 person-years).

*Conclusion:* Introducing ART has markedly reduced the risk of MAC for HIV-infected individuals with a history of very low CD4 counts. Survival after diagnosis of MAC has improved after ART became available. In patients responding to ART, discontinuation of maintenance therapy against *M. avium* may be safe.

*Key words: M. avium Complex; human immunodeficiency virus; antiretroviral combination therapy; incidence; survival; prognosis; discontinuation of maintenance therapy; secondary prophylaxis; cohort study*

## Introduction

Disseminated infection with *M. avium* Complex (MAC) is a frequent late complication of HIV-infection. During the natural course of HIV-infection up to 15% of patients will suffer from this opportunistic infection (OI) within 12 months after their CD4 count has fallen below 50 cells/mm$^3$ [1–3]. New regimes for treatment and primary prophylaxis were evaluated and proved beneficial in the early 1990's [4]. Nevertheless, incidence of MAC rose until 1993 (Figure 1) and the

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[2] The members of the Swiss HIV Cohort Study are listed in the appendix.

survival of patients with disseminated *M. avium* infection did not improve until 1996 in the Swiss HIV Cohort Study (SHCS) [3].

However, introduction of potent antiretroviral combination therapy (ART) in 1996 changed the natural history of HIV-infection. Patients on ART experience restoration of their immune system and have a lower risk of opportunistic infections thereafter [5, 6]. This decline in incidence may occur within the first three months of ART for some OIs, but for disseminated *M. avium* infection a significant reduction in risk is found only after 6 to 9 months of successful ART [7].

While mortality is markedly reduced in patients on ART, the effect on survival in patients having experienced serious specific late stage opportunistic infections is at present less well analysed. Many physicians care for patients surviving long term after having disseminated *M. avium* infection. In these patients it has to be decided whether maintenance therapy against recurrence of MAC is needed lifelong. Since primary prophylaxis against MAC and other opportunistic infections may be discontinued in patients with a sustained increase of their CD4 count [8–13] and discontinuation of maintenance therapy against *P. carinii* pneumonia and cytomegalovirus retinitis may be safe in certain circumstances [14, 15], some physicians and patients tend to interrupt maintenance therapy against *M. avium*, despite the limited evidence on the safety of this discontinuation [12, 16].

In the SHCS we addressed the issues of incidence and survival of disseminated *M. avium* infection before and in the era of ART, and the course of patients who interrupted maintenance therapy.

## Patients and methods

### The Swiss HIV Cohort Study (SHCS)

The SHCS enrols HIV-infected persons aged 16 years or older [17]. Patients are followed up in one of seven study centres. Enrolment is independent of disease stage and degree of immunodeficiency. Data are collected according to standardised criteria on structured forms at registration and at follow-up visits scheduled at 6 months intervals. AIDS is defined according to category C clinical conditions of the Centers for Disease Control and Prevention classification system for HIV infection (revised in 1993) [18]. Informed consent is obtained from all participants. The SHCS is representative for the epidemiology of advanced HIV-infection in Switzerland and includes approximately 70% of the patients diagnosed with AIDS in the country [19]. More detailed information is available online on http://www.shcs.ch.

### Analysis of incidence and survival rates of patients with disseminated *M. avium* infection

Patients with disseminated *M. avium* infection diagnosed between January 1990 and December 1999 were included in the analysis. According to the SHCS definition, diagnosis requires *M. avium* to have been cultured from tissue samples other than sputum, stool or skin and a concurrent illness consistent with the diagnosis, eg, weight loss, fever, diarrhoea or anaemia.

*Incidence rate of MAC:* Incidence density of disseminated *M. avium* infection was calculated year-wise by dividing the numbers of SHCS participants developing disseminated *M. avium* infection by the total follow-up time in the SHCS of all patients at risk. Only the first diagnosis of MAC in each patient was included. Since disseminated *M. avium* infection occurs nearly exclusively in patients with a CD4 cell count below 50cells/mm$^3$ only patients with former counts below this level contributed to the follow-up time. Patients with disseminated *M. avium* infection without a CD4 count measurement below 50 cells/mm$^3$ before diagnosis were not included in the calculation of incidence. Potent ART was introduced in the SHCS during 1996, and all patients had potential access to this treatment that was paid for by the obligatory health insurances. From 1997 onwards, antiretroviral treatment with at least 3 drugs was the most often prescribed regime (figure 1). Therefore, to assess influence of the availability of ART on disseminated *M. avium* infection, overall incidence from 1990 to 1996 was compared to the incidence thereafter. This ecological approach was chosen because it better represents the influence of the availability of ART on a population basis, than just comparing patients who did and did not receive ART. The latter type of comparison always leads to biased results, because those patients prescribed and taking ART differ sociodemographically from those that are not [20].

*Survival:* Patients within the SHCS that were diagnosed with disseminated *M. avium* infection in 1996 or later had access to potent ART with a protease-inhibitor based three drug regimen. To assess the influence of potent ART on mortality, we compared survival rates of patients with MAC before and after 1996. Patients with the diagnostic procedure at the day of death or with a post-mortem diagnosis were excluded from the survival analysis. Cox proportional hazards regression model including time-period of diagnosis of MAC, quartile of CD4 cell count at diagnosis, sex, age and transmission mode was performed to obtain the adjusted hazard ratio for the time-period. The real introduction of ART and the treatment of MAC for a single patient was not included in the model, because the time gap of drawing blood cultures for MAC and the results from cultures is usually several weeks. Therefore, patients with an a priori better prognosis, namely surviving at least 6 weeks, would have started these treatments with a greater probability. This would have biased the results of the model regarding these variables. In addition, as mentioned above, patients on potent ART differ sociodemographically from those who are not, in a manner that is difficult to correct for.

### Interruption of maintenance therapy against disseminated *M. avium* infection

The patients with a history of disseminated *M. avium* infection who stopped their maintenance therapy while on ART were identified within the SHCS database. A structured review of the records was undertaken for all of these patients: clinical and laboratory data at the time of diagnosis of MAC, at the time of starting ART, at the time of discontinuation maintenance therapy, and at the last follow-up visit were obtained. Incidence (with corresponding 95% confidence limits) of recurrence after discontinuation was

calculated by using the time period from discontinuation to the last follow-up or to the date of recurrence as a denominator and by assuming a Poisson distribution of events.

*Statistical analyses* included calculation of incidences with confidence intervals assuming a Poisson distribution of events, survival analyses using the Kaplan-Meier life-table method assessing the equality of the survival function by the log-rank test and Cox proportional hazards regression model. The proportional hazards assumptions were tested using Schoenfeld residuals. Non-parametric Wilcoxon rank sum test was used for comparison of numerical data between two unrelated groups. Stata software (version 7; Stata Corporation, College Station, Texas, USA) was used.

## Results

From 1990 to 1999 398 patients were diagnosed with disseminated *M. avium* infection within the SHCS. Distribution regarding gender (22% female) and transmission mode (39% men who had sex with men, 38% intravenous drug use, 21% heterosexual and 2% others) reflect the epidemiology of HIV-infection in the SHCS and in Switzerland. The median age and the corresponding interquartile range (IQR) was 34 years (IQR 30–40) and the median CD4 cell count at diagnosis was 10 cells/mm$^3$ (IQR 2–20). There was no statistically significant difference in age or CD4 count at diagnosis between the 320 patients diagnosed before 1996 and the 78 diagnosed thereafter.

### Incidence

350 (88%) patients with disseminated *M. avium* infection had a CD4 count below 50 cells/mm$^3$ measured before diagnosis. They were included in the calculation of incidence. A total of 3208 patients had a nadir CD4 count of less than 50 cells/mm$^3$ during the studied period and contributed to a total follow-up of 6004 person-years. Of these 3208 patients 24% percent were female, and transmission mode was men who had sex with men in 36%, intravenous drug use in 37%, heterosexual in 23% and others in 4%. The incidence over the whole study period was 5.8 events per 100 person-years. The incidence per year is shown in figure 1. From 1990 until the end of 1996 during a total follow-up time of 3563 person-years, there were 315 episodes of disseminated *M. avium* infection resulting in an incidence of 8.8 per 100 person-years (95% confidence interval 7.9–9.8) compared to 35 cases during a total follow-up time of 2441 person-years (incidence 1.4 per 100 person-

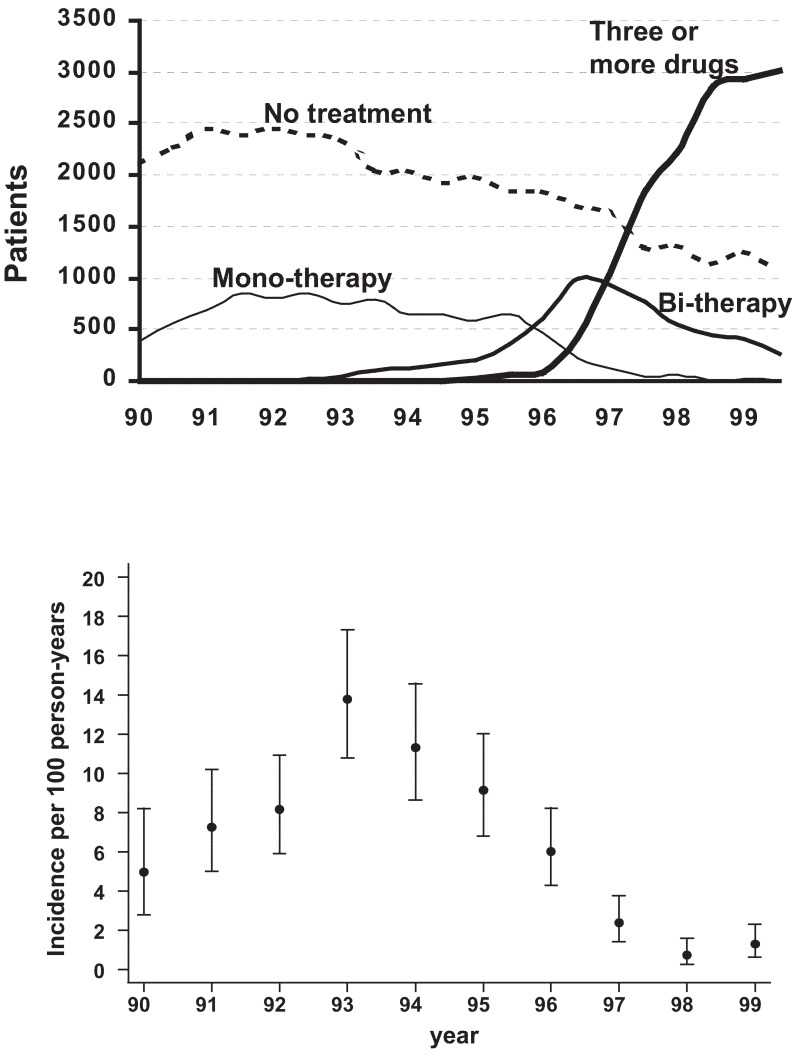



**Figure 1**

Use of antiretroviral drug regimes within the Swiss HIV Cohort Study (top panel) and incidence density of disseminated *M. avium* Complex infection (cases per 100 person-years) in patients with a nadir CD4 cell count below 50 cells per mm$^3$ from 1990 to 1999 (bottom panel). The percentages of patients on at least 3 antiretroviral drugs were 13% in the middle of 1996, 48% in the middle of 1997, 65% in the middle of 1998, and 71% in the middle of 1999. The respective percentages for patients with a nadir CD4 count below 50 cells per mm$^3$ were 55% (1996), 75% (1997), 80% (1998), and 84% (1999).

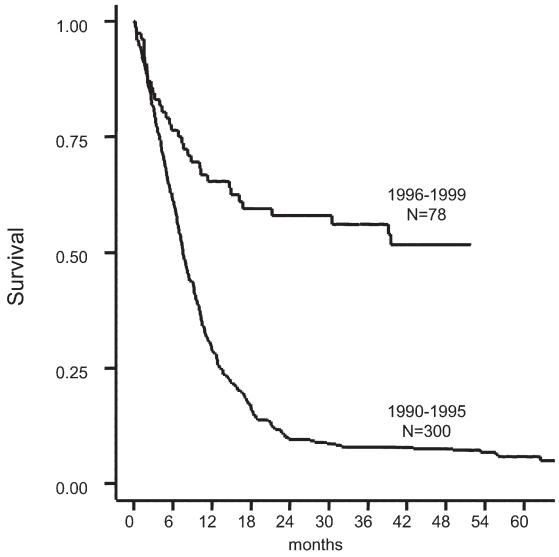



**Figure 2**

Kaplan Meier curve of survival after diagnosis with disseminated *M. avium* Complex infection in AIDS patients enrolled in the Swiss HIV Cohort Study according to the time period of availability of potent antiretroviral combination therapy. These regimen were not available before 1996.

years; 95% CI 1.0–1.9) from 1997 until 1999. This corresponds to a decrease in incidence of 7.4 per 100 person-years (95% CI 6.3–8.4) or an incidence ratio of 0.16 (95% CI 0.11–0.23) which is highly significant (p <0.001). The highest incidence was observed in 1993 with a rate of 13.7 events per 100 person-years (95% CI 10.7–17.3), whereas the lowest incidence was 0.73 events per 100 person-years (95% CI 0.26–1.5) in 1998.

### Survival

Twenty patients (5%) were excluded from the survival analysis because diagnosis of disseminated *M. avium* infection was made at the day of death or post-mortem. All these patients were diagnosed before 1996. 378 patients were thus included in the survival analysis. Figure 2 shows Kaplan Meier estimates of survival after diagnosis of disseminated *M. avium* infection in 300 patients diagnosed before 1996 compared to 78 that were diagnosed from 1996 to 1999. Survival improved significantly (p <0.001 by log rank test) after introduction of potent ART. A Cox proportional hazards model including time period of diagnosis, sex, transmission mode, quartile of CD4 count at diagnosis and age was used to look at and correct for confounding factors. In this model the time period of diagnosis (1996–1999 versus 1990–1995) remained the most powerful predictor for survival (table 1).

### Interruption of maintenance therapy

The 24 patients who had interrupted maintenance therapy were identified using the SHCS database. Baseline and follow-up characteristics of these patients are shown in table 2. Stopping suppression therapy was proposed by the treating physicians of 12 patients. Another ten patients wished themselves to cease therapy, in two cases the reason for stopping could not be determined.

Figure 3 shows the absolute CD4 cell count values during follow-up of the patients discontinuing maintenance therapy.

During the observed period of 56.6 person-years, no recurrences of MAC were clinically documented. In addition, negative control blood cultures confirmed absence of *M. avium* Complex bacteraemia in eleven patients. The median follow-up time was 29 months (range 11 to 50 months). The upper 95% confidence level of incidence was 5.3 events per 100 person-years.

Two patients died during the follow-up period. One patient with end stage liver cirrhosis due to hepatitis C had a fatal pneumonia and one patient died of an invasive bacteraemic infection with *S. aureus*.

## Discussion

Introduction of antiretroviral combination therapy has markedly changed the natural history of HIV-infection in developed countries. Morbidity and mortality have declined [5, 6].

Disseminated *M. avium* infection is a typical opportunistic infection occurring mainly in stages of profound immunodeficiency during HIV-infection [1, 3, 21] as shown by the median CD4 count of only 10 cells/mm$^3$ at baseline in the current analysis of the SHCS. Median survival after this opportunistic infection has been below one year even after introduction of antimycobacterial combination chemotherapy including newer macrolides in the mid nineties [2, 3, 22–25].

Primary prophylaxis against MAC with azithromycine, clarithromycine or rifabutin has proven beneficial in patients at high risk for this complication indicated by CD4 counts below 50 cells/mm$^3$ [4, 26, 27]. However, primary prophylaxis against MAC has not been widely used within the SHCS [8]. Despite only moderate efficacy of about 50% risk reduction [27], availability of this prophylaxis after 1993 could explain in part the subsequent decline of the incidence rate of MAC in the SHCS.

The risk of MAC in an individual patient with low CD4 counts remains high during the first three months of ART and declines sharply thereafter if the CD4 count rises to above 100 cells/mm$^3$ [7], allowing withdrawal of antimycobacterial prophylaxis against this pathogen [8, 10, 28]. On a population level the present analysis shows that during the time period when ART became available, there was a major influence on the incidence of MAC. Our results are in concordance with the recently published analysis of the EuroSIDA cohort which demonstrated that the risk of disseminated MAC decreased with increasing calendar time after 1995 [29].

One might argue that the incidence declined because the risk of exposure to this pathogen decreased during the same period. Since *M. avium* is an ubiquitous micro-organism there is no evidence for such a bias [30]. In addition the laboratory meth-

**Table 1**

Hazard ratio of death according to a Cox proportional hazards regression model in 378 patients with a diagnosis of disseminated *M. avium* infection.

| Parameter | | Crude hazard ratio (95% CI) | Adjusted hazard ratio* (95% CI) |
|---|---|---|---|
| Time period of diagnosis (1996–1999 versus 1990–1995) | | 0.29 (0.20–0.41) p <0.001 | 0.27 (0.18–0.39) p <0.001 |
| CD4 count quartile (per quartile increase)** | | 0.92 (0.83–1.03) p = 0.16 | 0.89 (0.81–0.99) p = 0.04 |
| Female sex | | 0.79 (0.61–1.04) p = 0.1 | 0.98 (0.71–1.34) p = 0.9 |
| Transmission risk group as compared to MSM | | | |
| | Heterosexual | 0.72 (0.53–0.98) p = 0.04 | 0.86 (0.60–1.23) p = 0.9 |
| | IDU | 0.858 (0.62–1.15) p = 0.2 | 1.05 (0.79–1.40) p = 0.7 |
| | Others | 0.78 (0.33–1.79) p = 0.5 | 0.82 (0.40–1.70) p = 0.6 |
| Age quartile (per quartile increase) | | 1.08 (0.98–1.19) p = 0.13 | 1.11 (0.99–1.25) p = 0.07 |

* adjusted for all the variables listed

** CD4 count quartiles represent the studied population stratified by CD counts, the first quartile is the quarter of the studied population with the lowest CD4 counts, the second quartile the quarter of the population with CD4 counts between the 25th percentile and the median and so on. The CD4 at the respective quartile limits are described in the results section.

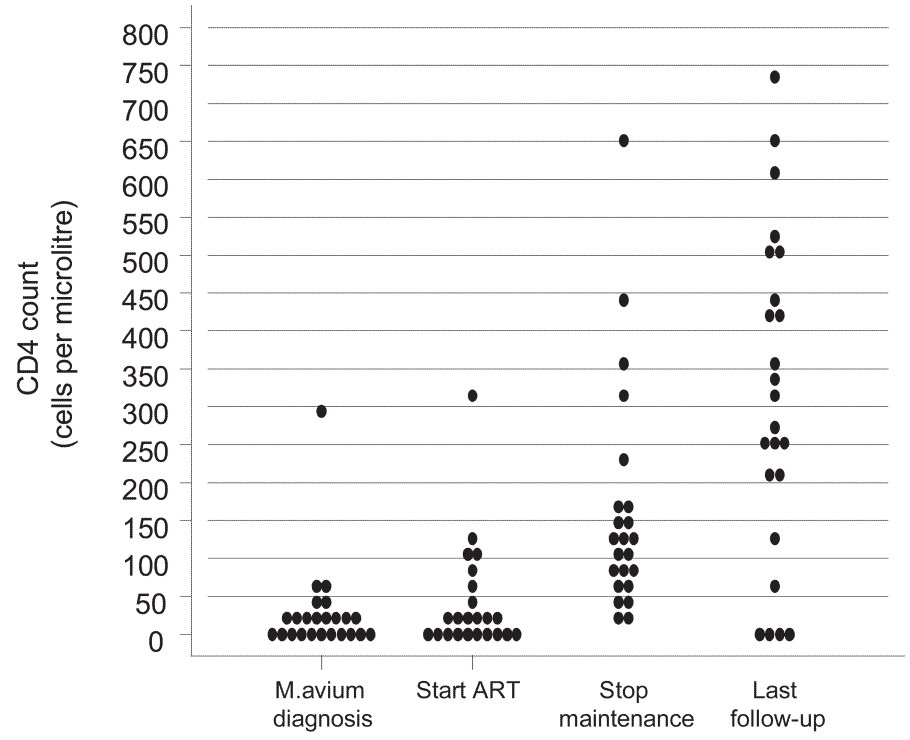
**Table 2**

Characteristics and follow-up data of 24 patients who discontinued maintenance therapy against *M. avium* (median, range).

| | Diagnosis of MAC | start ART | stop MAC-suppression | last follow-up |
|---|---|---|---|---|
| Age | 32 (22–50) | | | |
| Weight (kg) | 60 (43–74) | 58 (43–74) | 65 (48–76) | 67 (48–81) |
| Haemoglobin (g/l) | 98 (64–134) | 103 (81–139) | 129 (99–150) | 142 (100–181) |
| CD4 Cell Count cells/mm$^3$ | 11 (0–304) | 14 (2–315) | 127 (27–644) | 291 (1–740) |
| Percentage of CD4 cells of total lymphocyte count | 3 (0–23) | 4 (1–29) | 14 (3–29) | 18 (1–33) |
| HIV RNA (log10 copies/ml) | 5.3 (2.3–6.4) | 5.7 (0.6–6.3) | 3.6 (0.6–5.9) | 2.6 (0.6–6.0) |

**Figure 3**

Absolute CD4 counts of 24 patients discontinuing maintenance therapy against *M. avium*.



ods for culture and identification of mycobacteria have improved within the last ten years and physicians are still well aware of the clinical presentation of MAC making detection bias highly improbable.

ART results in restitution of specific memory immune response against pathogens to which patients are chronically exposed [31–34]. This may lead to marked inflammatory responses within a few weeks after starting ART [35–39]. *M. avium* is a micro-organism with low virulence but leads to high bacterial burden in disseminated disease. Therefore, in addition to antimycobacterial drugs an even moderately strengthened immune system will probably be important to overcome chronic progressive infection and disease. In fact, there are AIDS patients recovering from *M. avium* bacteremia who have only started ART, without the need for additional antimycobacterial drugs [40].

In the present analysis, being diagnosed with disseminated MAC during the period after potent ART became available is an impressively strong predictor of a better survival. Median survival of disseminated MAC changed from about seven months before 1996 to more than four years thereafter. The ecological population based approach of including the availability of ART instead of successful antiretroviral treatment as a parameter in the model of survival is a conservative one. The real effect of taking ART may be still stronger. In fact, patients diagnosed after 1995 who never started potent ART had a median survival of less than seven months. However, given the imminent biases of comparisons of patients on ART to those not on ART, the chosen strategy of analysis is the one closest to an intention to treat approach.

Until recently there was little evidence supporting the discontinuation of maintenance therapy against opportunistic infections [12]. However, more and more observational studies describe successful interruption of secondary prophylaxis against eg, *P.carinii* or cytomegalovirus [13]. Given the relatively low virulence of *M. avium* such an approach should be possible in disseminated *M. avium* infection once a certain immune-restitution has taken place [16]. Discontinuation is still more appealing taking into account the side effects, costs and global resistance driving forces of antimycobacterial combination therapy.

In the current analysis we identified no recurrence of MAC disease in patients who had stopped taking maintenance therapy against MAC while on ART. The upper confidence limit for incidence of recurrence of more than 5 per 100 person-years, however, precludes from stating that this approach is very safe. In addition, retrospective review of medical records for analysis of prospectively collected cohort data does not allow definition of a CD4 threshold level above which stopping maintenance therapy can be considered as safe. The median CD4 count at the time of discontinuation was slightly above 100 cells/mm$^3$ in the patients studied. However, the group of patients that interrupted therapy was very heterogenous and included four patients with a CD4 count of less than 50cells/mm$^3$. A sustained increase to at least 100 cells/mm$^3$ has proven safe for stopping primary prophylaxis [8]. It might well be a valuable threshold level for discontinuing maintenance therapy.

In conclusion, introduction of potent antiretroviral combination therapy has markedly reduced the risk of disseminated MAC infection for HIV-infected individuals with a history of very low CD4 counts. Furthermore, survival after a diagnosis of disseminated MAC infection has improved since antiretroviral combination therapy became available. In patients surviving this disease and responding to antiretroviral treatment, discontinuation of maintenance therapy against *M. avium* seems to be possible and should be studied prospectively.

## Appendix

The members of the Swiss HIV Cohort Study are M. Battegay (Chairman of the Scientific Board), E. Bernasconi, H. Bucher, Ph. Bürgisser, M. Egger, P. Erb, W. Fierz, M. Flepp (Chairman of the Clinical and Laboratory Committee), P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne), H. Furrer, M. Gorgievski, H. Günthard, P. Grob, B. Hirschel, Th. Klimkait, B. Ledergerber, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, J.-C. Piffaretti, M. Rickenbach (Head of Data Center), C. Rudin, P. Sudre, V. Schiffer, J. Schupbach, A. Telenti, P. Vernazza, Th. Wagels, R. Weber

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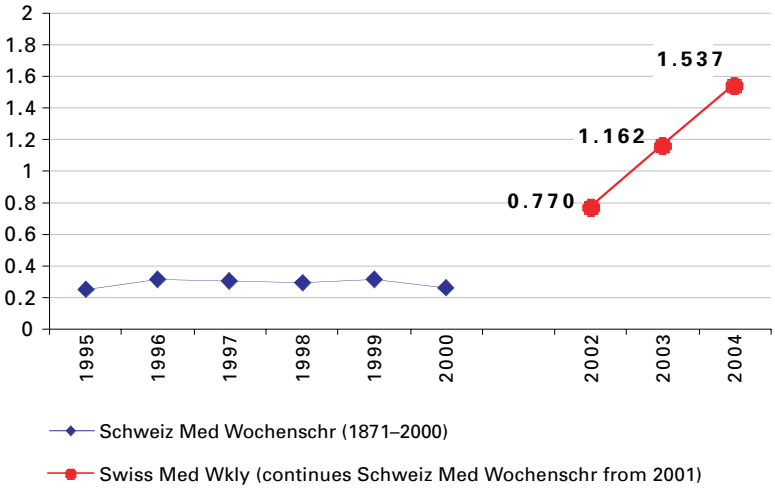


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