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Discontinuation of Prophylaxis against Opportunistic Infections in HIV-Infected Persons Receiving Potent Combination Antiretroviral Therapy

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Abstract

Prophylaxis and maintenance therapy against opportunistic infections (OI) are a mainstay in the management of HIV-infected patients and have led to a significant improvement in the quality of life and survival. In the past few years potent combination antiretroviral therapy became available. This treatment leads to an improvement in the immune function and is associated with a marked decrease in the incidence of opportunistic infections. This has raised the question whether primary or secondary prophylactic therapies may be discontinued without the risk of new or recurrent OI's. This issue is being addressed by several study groups. For each opportunistic infection, parameters that might influence the decision to discontinue primary or secondary prophylaxis should be clearly defined and evaluated. Stopping primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with a sustained rise in CD4-lymphocyte count above 200/µL has proven safe. Discontinuation of primary prophylaxis against *Mycobacterium avium* disease and of maintenance therapy against cytomegalovirus retinitis might also be safe in certain patients receiving potent combination antiretroviral therapy.

Key words

Opportunistic infections. Prophylaxis. HAART. Maintenance therapy. Immune restoration.

Rationale for prophylaxis and maintenance therapy against opportunistic infections

During the first decade of the HIV-epidemic introduction of primary prophylaxis against opportunistic infections (OI) such as *Pneumocystis carinii* pneumonia (PCP), toxoplasmic encephalitis, disseminated *M. avium* infection and bacterial infections led to a significant improvement in the quality of life and survival of HIV infected persons[1-6]. The concept of providing primary prophylaxis was mainly based on the association of threshold reductions in peripheral blood CD4-lymphocyte numbers with risk for developing specific infections[7,8]. For example, the risk of PCP was found to markedly increase as peripheral blood CD4 counts dropped below 200 cells/µL and 14% of total lymphocytes[9,10] Thus, CD4-lymphocyte threshold levels could be defined as indi-

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cators of risk for specific OI's, and in some instances randomised trials supported the rationale of initiating primary prophylaxis for some of the most prevalent OI's when CD4 counts declined below these threshold values (Fig. 1A)[11]. In general, primary prophylaxis should be considered if a specific OI has a high incidence, is associated with considerable morbidity and/or mortality, and if a prophylactic agent is available, that is, effective, well tolerated and has acceptable cost benefit ratio[12]. Cotrimoxazole prophylaxis for PCP, toxoplasmic encephalitis and bacterial infections is the perfect example of such an agent.

In AIDS patients most of the OI's have a high recurrence rate after successful treatment of the acute episode. Therefore, lifelong maintenance therapy (also called secondary prophylaxis) is usually indicated to prevent recurrent disease (Fig. 1B)[11]. The only OI for which prophylaxis and maintenance therapy of limited duration has proved effective is tuberculosis.

Changing course of HIV infection in the era of potent combination antiretroviral therapy

The introduction of combination antiretroviral therapy, double nucleoside reverse transcriptase inhibitors (NRTI) combination after 1994[13-15] and triple combination, including in addition at least one protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI), after 1996[16] was associated with an impressive decline in morbidity and mortality of HIV-infected persons not only in controlled trials but also in population based epidemiological surveillance studies (Fig. 2)[17-21].

Combination antiretroviral therapy (ART) leads to inhibition of viral replication resulting in a decline of measurable plasma HIV-RNA levels below the limit of detection and to an increase of CD4-cell counts in a majority of patients[22]. The CD4 count increase is most significantly associated with the decline in incidence for new opportunistic infections[23].

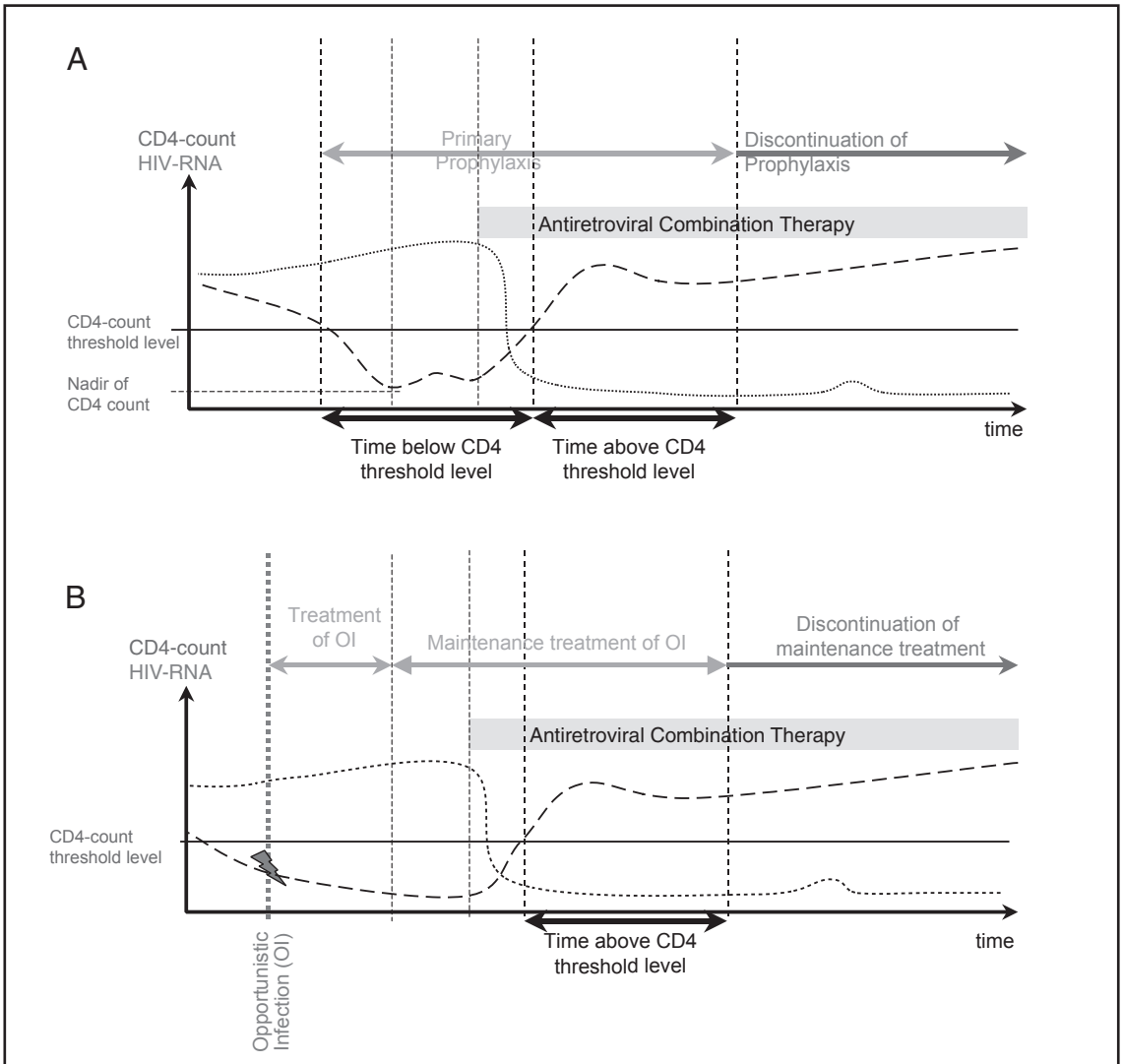

Fig. 1. *Time dependent parameters for introduction and discontinuation of primary prophylaxis (Fig. 1A) and maintenance therapy (Fig. 1B) for opportunistic infections in the course of HIV-infection: CD4 lymphocyte count (…), Plasma HIV-RNA (---).*

As a result, many patients experience rises in CD4 cell numbers above the formerly determined thresholds for instituting primary prophylaxis. This has raised the question whether primary or even secondary prophylactic therapies may be discontinued without exposing such patients to the risk of new or recurrent OI's[24].

Parameters that might influence the decision to discontinue primary or secondary prophylaxis

Criteria for prophylaxis discontinuation may be based on several pathophysiological considerations which are graphically illustrated in (Fig. 1A and 1B) for primary prophylaxis and maintenance treatment, respectively.

a) Effectiveness and safety of prophylactic regimens

Prospective studies yielding meaningful results are only possible for OI's with a high prevalence, and for which well defined guidelines for instituting primary and secondary prophylaxis have been formulated, such as PCP, toxoplasmic encephalitis, disseminated *M. avium* infection and cytomegalovirus (CMV) retinitis[11]. Ideally recommendations on discontinuing prophylaxis and/or maintenance for specific OI's should be based on placebo controlled trials showing an equivalently low incidence of OI's after discontinuation or continuation of the respective regimens. However, the incidence of OI's in patients after the first 3 to 6 months of successful combination antiretroviral therapies has been observed to be very low[23]. Thus, many clinicians are in favour of comparing the results of prospective observational studies with historical cohort data of OI incidence in patients receiving primary and secondary prophylaxis[25]

Furthermore, many patients and their physicians make the decision to discontinue prophylaxis without enrolling the patients in study protocols. Results of such practice are more difficult to analyse, but meaningful results can eventually be obtained from well performed cohort analysis[26].

The decision to discontinue prophylaxis or maintenance treatment may be more easily made if the respective regimen is associated with considerable side-effects and costs and is negatively affecting quality of life, as is the case with intravenous maintenance therapy for CMV retinitis, or primary and secondary prophylaxis for *M. avium* infection. In contrast, the decision to discontinue a convenient, highly effective and inexpensive prophylaxis such as cotrimoxazole for PCP may demand a higher level of certainty that this can be done without an unacceptable risk of PCP occurrence/recurrence.

Finally, physicians may be more easily inclined to discontinue prophylaxis or maintenance treatment against less severe OI's which can be diagnosed early and treated easily such as oropharyngeal *Candidiasis* or recurrent mucocutaneous *Herpes simplex* infection.

b) Immune restoration in patients on combination antiretroviral therapy: CD4 count, CD4 percentage, nadir of CD4 count

The most widely used surrogate marker for immunocompetence in HIV-infected patients is CD4 lymphocyte *count* in peripheral blood[7]. This measurement has proved useful during the natural course of HIV infection. However, it is unclear whether this measurement indicates effective immunocompetence during immune restoration on ART[27]. Indeed, CD4 cell counts usually increase steeply during the first few weeks of ART but the incidence of OI's only significantly declines after 3 to 6 months[23,28]. This initial CD4 cell rise has been explained by a redistribution of CD4 cells, sequestered in lymphoid tissue to the peripheral blood[29]. These early reappearing CD4 and CD8 T lymphocytes consist mainly of pre-existing memory cells and their immune repertoire does not seem to be significantly broadened[27,30]. Nevertheless, early on there seems to be an enhanced lymphoproliferative activity against antigens to which the majority of patients have been previously exposed, such as *Candida*, CMV or mycobacteria[30,31], explaining in part the reports of immunopathogenic reactions against pathogens shortly after starting ART[32-34].

After 3 to 6 months of ART functional immune reconstitution has been documented *in vitro*[30,31,35]. After about 6 months there is also an increase in naïve T-cells and the immune repertoire tends to normalise[36]. These *in vitro* results correlate nicely with epidemiological observations of a decline in incidence of new OI's (Fig. 3)[23]. This decline in incidence is significantly associated with the rise in CD4 counts. An increase of 50 cells/μL after 6 months of ART leads to a risk reduction of 70% for a new AIDS defining event in a multivariate model. In practical terms, reaching a level of 200 cells/μL after initiation of ART predicts a significant degree of protection from OI's[23]. These observations have led most experts to recommend a period of 3 to 6 months of CD4 counts above the respective threshold level before prophylaxis should be discontinued in prospective studies[37].

CD4 cell percentage of total peripheral lymphocyte count is an independent risk factor for PCP[10]. Some investigators therefore define a threshold level for this parameter in addition to the absolute CD4-cell count[25]. Whether this additional parameter is necessary will only be shown in the future.

Immune reconstitution is broader and more rapid in patients treated before severe immune depletion has occurred[38]. The baseline CD4 cell count remains an independent predictor for the risk of OI's after initiation of ART. Compared to a CD4 cell count above 200/μL, the hazard ratio for the occurrence of new OI's was 5.8 for counts below 50 cell/μL at baseline[23]. Therefore the nadir CD4 count as well as the time spent below the threshold level (Fig. 1A) could represent additional parameters to be used when judging the risk of discontinuing primary prophylaxis. Subgroup analysis for patients with very low nadir CD4 counts should therefore be per-

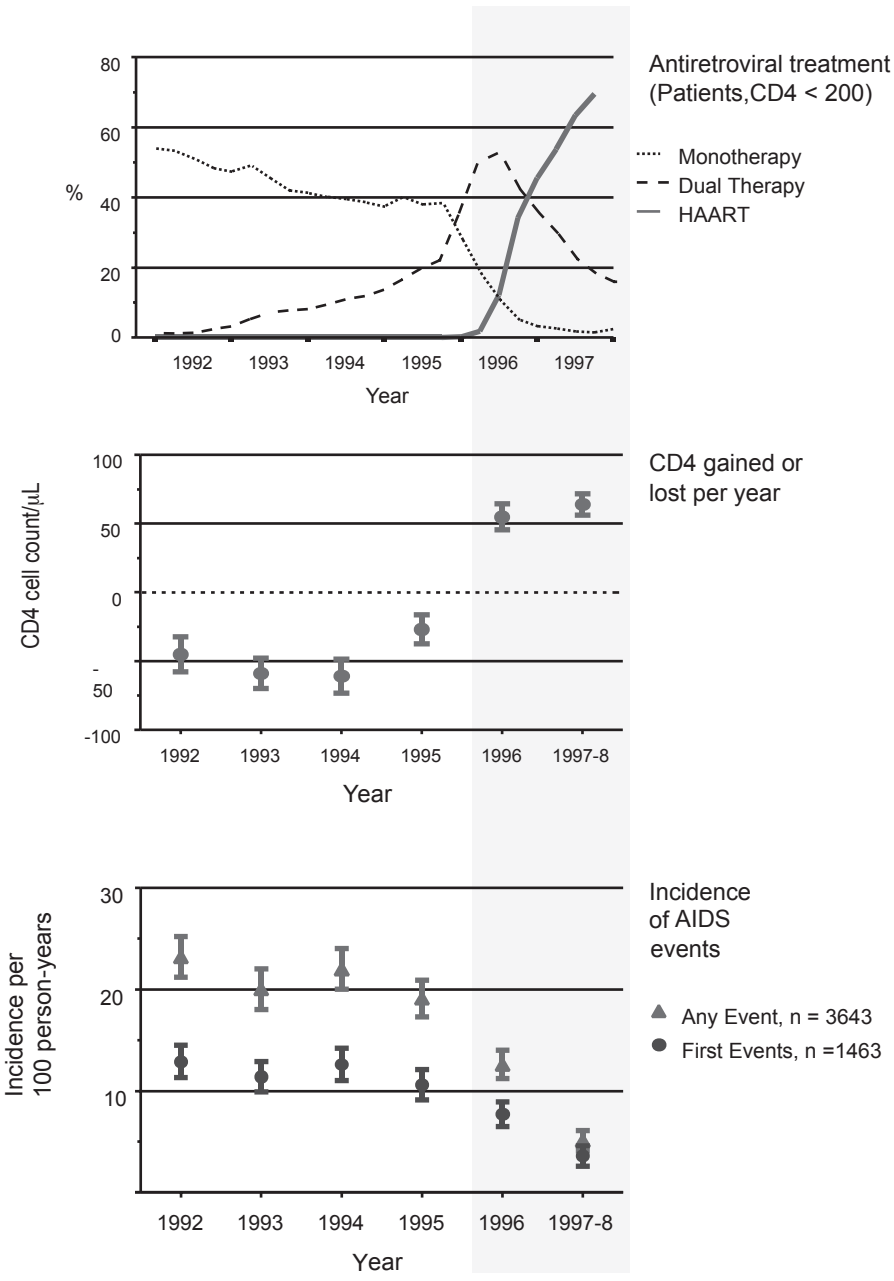

Fig. 2. *Change in the course of HIV infection in the era of combination antiretroviral therapy (1992-1998). Data from the Swiss HIV-Cohort study (adapted with permission from[58]): Antiretroviral regimens in patients with nadir CD4 count below 200 cells/µL (upper), CD4 counts lost or gained per year (mean +/-SD) (middle) and Incidence of AIDS defining events (lower).*

formed in the large studies of discontinuation of primary prophylaxis to prove the safety also for this population.

c) Virologic response: HIV-RNA

In successful ART there is a rapid decline of viral load measured by plasma HIV-RNA to less than 400 or even 50 copies per mL within 3 months[39]. Resurgence of viral load above these levels is considered as virologic failure and may be associated with the appearance of HIV isolates, which are resistant to the antiretroviral drugs which were prescribed[40,41].

However, most of the patients with virological failure to ART continue to profit clinically from antiretroviral therapy, at least as long as their CD4 cell counts stay above the threshold levels for developing OI's[42-44]. This may be the case for several years. Analysis of immune function and of viral fitness parameters explains the net benefit from antiretroviral therapy despite suboptimal control of viral replication[45].

Active HIV replication may be associated with an altered cytokine and chemokine milieu that may hamper immune responses to OI antigens[31,46]. Whether this is true, and especially whether this is clinically significant, can only be shown in the future, comparing incidences of OI's in patients with

different virological responses and correcting for CD4 counts. Data from trials before the era of potent ART showed an independent association between reductions of viral load and reduction of incidence of PCP, CMV and MAC disease[47]. Achieving suppression of viremia after 6 months of ART leads to a risk reduction for OI's of 61% and predicts a significant degree of protection from OI's[23].

In the absence of more data, several experts recommend discontinuing prophylaxis only when both an adequate CD4 cell and HIV-RNA response are present and reintroducing prophylaxis if subseqent virological failure occurs, even if the CD4 cell response is still maintained. Whether such an approach is necessary warrants further study.

Discontinuation of prophylaxis and maintenance therapy against specific opportunistic infections

a) Pneumocystis carinii pneumonia

Discontinuation of primary prophylaxis. Primary prophylaxis against PCP is indicated in patients whose CD4 cell counts fall below 200 cells/μL or below 14% of total lymphocyte count[37].

The results from two prospective observational studies[25,48], one randomised controlled trial[49] as well as from retrospective analyses involving large cohorts[26,50] addressing the discontinuation of primary PCP prophylaxis in the context of potent combination ART-associated rises in CD4 cell counts have been published or presented recently. Inclusion criteria in the prospective studies generally were a rise of CD4 cell counts above 200/μL sustained for at least three months. The largest study also required a sustained rise of CD4 cell percentage to at least 14%[25]. In this study there were no cases of PCP during the follow-up period of 238 patient years, resulting in an upper 99% confidence interval of incidence of less than 2 % patient years. The median follow-up period was less than one year and median nadir of CD4 cell count was about 110 cells/μL. More than half of the patients had plasma viral load of less than 400 copies per mL and CD4 counts of more than 300 cells/μL at the time of discontinuation. All other studies have essentially confirmed this extremely low incidence of PCP following the discontinuation of primary PCP prophylaxis. Therefore, discontinuation of primary PCP prophylaxis seems safe in patients with a sustained rise of the CD4 cell count to above the currently generally accepted CD4 threshold for instituting prophylaxis. Whether this policy is also pertinent for patients with very low prior CD4 cell nadirs or for patients with more obvious degrees of virologic failure will need to be addressed in future subgroup analyses within the ongoing studies. Most investigators recommend reintroducing primary PCP prophylaxis if CD4 cell counts again drop below the above mentioned threshold values.

Discontinuation of secondary prophylaxis. The studies reported so far have not included sufficient patients stopping secondary PCP prophylaxis to rule out an unacceptable risk of recurrence of PCP. Although discontinuation of secondary PCP prophylaxis may be safe, this should preferably be done within the context of studies addressing this particular question.

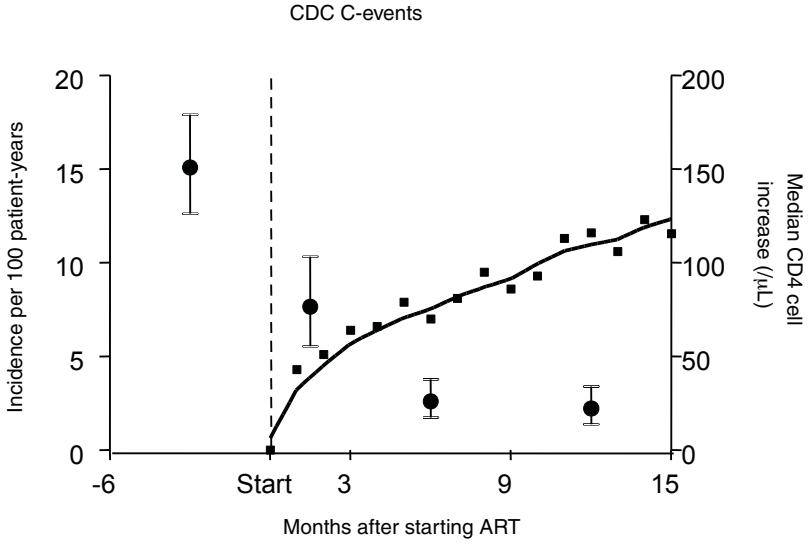

Fig. 3. *Decline in the incidence of AIDS-defining opportunistic events (left y-axis) and median increase of CD4-lymphocyte count (black squares, right y-axis) in the 6 months after patients began antiretroviral combination therapy compared to the previous 3 and 6 months periods. The decline in incidence and the increase of CD4 lymphocyte count is statistically significant (p < 0.001). (Swiss HIV Cohort Study, unpublished data, courtesy of B. Ledergerber, Zurich).*

b) Toxoplasmic encephalitis

Discontinuation of primary prophylaxis. Primary prophylaxis against toxoplasmic encephalitis (TE) is indicated in patients who are seropositive for *Toxoplasma gondii* and have CD4 counts below 100 (US guidelines) or 200/μL (some European guidelines)[37].

One study evaluating the safety of discontinuation of primary PCP prophylaxis with cotrimoxazole also prospectively addressed the safety of discontinuing this agent for primary TE prophylaxis in the subgroup of patients that were seropositive for *Toxoplasma gondii*. Criteria for discontinuation were CD4 counts of at least 200/μL and 14% for more than 12 weeks. The outcome was evaluated in 121 toxoplasma antibody positive patients with a total follow-up of 110 patient years. Not a single case of TE was observed during follow-up. The upper 99% confidence limit of this zero-incidence rate was 4.2 % patient years (upper 95% confidence limit 2.7 % patient years)[25]. Therefore, discontinuation of primary prophylaxis against TE may be safe if the entry criteria of this study are applied. However, further follow-up is needed to exclude an incidence risk of more than 2 % patient years.

Discontinuation of maintenance treatment. There are no data about the safety of discontinuation of maintenance treatment against TE. Given the particularly serious morbidity of recurrent TE, the discontinuation of maintenance therapy for TE should not be considered lightly and should be the topic of future prospective studies.

c) Disseminated *M.* avium *infection*

Discontinuation of primary prophylaxis. According to current guidelines, prophylaxis for disseminated MAC infection is indicated for HIV-infected patients with CD4 cell counts of less than 50/μL.

The incidence of disseminated MAC infection is very low after 6 months of successful potent combination antiretroviral treatment even in the absence of primary prophylaxis. As yet unpublished observational data presented at a major international conference indicate that stopping primary prophylaxis after a rise of CD4 cell count above 100/μL for 6 months may be safe[50].

Discontinuation of maintenance therapy. There are only a few case reports about stopping maintenance therapy in patients whose CD4 counts rise above 200 cells/μL[51]. Results of larger surveys are needed before a recommendation about discontinuation of maintenance therapy can be given.

d) CMV retinitis

Discontinuation of primary prophylaxis. Primary prophylaxis with oral ganciclovir against CMV disease, although proven to have some efficacy, has not become standard of care, given the side effects, and high pill burden and cost of this intervention. A preemptive therapeutic approach involving more promising drugs than oral ganciclovir may be considered in patients with CD4 counts below 50 cells/μL who have documented CMV viremia by PCR and are unable to take potent combination ART or have failed such treatment[52]. However, this strategy has not yet been tested in a prospective trial. Successful ART should lead to a stop of primary prophylaxis with oral ganciclovir.

Discontinuation of maintenance therapy. Intravenous maintenance therapy for CMV disease has major side effects negatively affects quality of life and is associated with considerable costs. For this reason, several investigators are assessing the safety of stopping CMV maintenance therapy in patients receiving successful potent combination ART leading to a rise in CD4 counts to above 150/μL for several months and undetectable HIV viral load in plasma[53,54]. Preliminary results of these studies indicate that the recurrence rate of CMV retinitis is very low the first 6 to 20 months[55,56]. The risk of recurrence seems to be higher in patients with detectable CMV viremia by PCR, HIV virologic failure to therapy and a lack of restoration of CMV specific immunity *in vitro*[57]. Thus, these latter indicators as well as the CD4 cell number, may need to be taken into account when deciding whether or not to discontinue secondary prophylaxis for CMV.

For the time being, patients should preferably be enrolled into studies to assess the safety of discontinuation. The decision of discontinuation should be made jointly with an experienced ophthalmologist also taking into account the anatomic location of prior CMV retinitis lesions, whether only one or both eyes are affected, and the current visual function. If maintenance treatment is discontinued, regular ophthalmologic consultation should verify the lack of reactivation of CMV retinitis. Maintenance treatment should be reintroduced if the CD4 cell count falls below 50-100 cells/μL[37]. Alternatively, among patients whose CD4 counts subsequently drop, reintroduction of CMV treatment may be postponed in those with only prior peripheral retinal lesions, if frequent ophthalmologic monitoring does not show evidence of disease reactivation.

e) Other OI's

Discontinuation of primary prophylaxis. There are no generally recommended indications for primary chemoprophylaxis for other OI's in HIV-infection.

Discontinuation of maintenance therapy. There are no data concerning the safety of stopping maintenance treatment for other OI's. OI's worthwhile to be studied are the invasive fungal infections like *Cryptococcosis*, *Histoplasmosis* and *Coccidiomycosis*, as well as recurrent *septicaemia* with *Salmonella spp*.

Withdrawal of secondary prophylaxis for recurrent oropharyngeal or oesophageal candidiasis and recurrent mucocutaneous *Herpes simplex* virus could also be the topic of an interesting study. Given the less serious nature of these latter infections, it is likely that secondary prophylaxis for these latter infections are already frequently being discontinued, and careful observational studies may yield

Table 1. *Discontinuation of primary prophylaxis or maintenance therapy for selected specific infections. (Adapted from[37]).*

Opportunistic infection		Indication for initiating prophylaxis	Safety of discontinuation*	Criteria for Discontinuation	Criteria for restarting prophylaxis
Pneumocystis carinii pneumonia	Primary prophylaxis	CD4 < 200 cells/µL or < 14% or clinical evidence for significant immunodepletion	+++	CD4 > 200 cells/µL and >14% for >12 weeks	Same as for initiating
	Maintenance therapy	History of PCP	n.a.	n.a.	n.a.
Toxoplasmic encephalitis	Primary prophylaxis	CD4 < 200 (100) cells/µL and positive serology for *T .gondii*	++	CD4 >200 cells/µL and >14% for >12 weeks	Same as for initiating
	Maintenance therapy	History of toxoplasmic encephalits	n.a.	n.a.	n.a.
Disseminated *M. avium* infection	Primary prophylaxis	CD4 < 50 cells/µL	+	Not well defined, CD4 >100 for >24 weeks	Same as for intiating
	Maintenance therapy	History of disseminated *M. avium* infection	+	Not well defined, CD4 > 200/µL for 24 weeks and completion of at least one year of effective antimycobacterial therapy	CD4 < 50 cells/µL
Cytomegalovirus retinitis	Primary prophylaxis	Not well defined	n.a.	Successful ART for >12 weeks	
	Maintenance therapy	History of Cytomegalovirus retinits	+	Not well defined, possible: No active lesion, no CMV viremia, adequate vision of contralateral eye, regular ophthalmic examination, no active extraocular CMV disease	CD4 < 100 cells/µL

*criteria for safety of discontinuation: +++ = concordant results in several published prospective studies with sufficient follow-up. **++** = at least one published prospective study with sufficient follow-up. **+** several published or presented data but no prospective study or insufficient follow-up. n.a. = not available.

Table 2. *Ongoing prospective studies on discontinuation of primary prophylaxis and maintenance therapy.*

Opportunistic infection	Discontinuation	Study name, study team, country	Design, Inclusion criteria
Pneumocystis carinii pneumonia	Primary prophylaxis	Stopcox1 (Swiss HIV Cohort Study), Switzerland	Prospective observational, CD4 > 200 and 14% for at least 12 weeks
		Gesida, Spain	Randomised trial, CD > 200 and HIV RNA < 5000 for at least 3 months
		Schneider *et al*, The Netherlands	Prospective observational, CD4 > 200 for at least 12 weeks
		ACTG 888, USA	Prospective observational, CD4 > 200 for at least 12 weeks
		EuroSIDA, pan-European plus Israel	Prospective observational, individual decision, no strict criteria
	Maintenance therapy	Stopcox2 (Swiss HIV Cohort Study), Switzerland	Prospective observational, CD4 > 200 and 14% for at least 12 weeks
		Gesida, Spain	Randomised trial, CD4 > 200 and HIV RNA < 5000 for at least 3 months
		Schneider *et al*, The Netherlands	Prospective observational, CD4 > 200 for at least 12 weeks
		ACTG 888, USA	Prospective observational, CD4 > 200 for at least 12 weeks
		EuroSIDA, pan-European plus Israel	Prospective observational, individual decision, no strict criteria
Toxoplasmic encephalitis	Primary prophylaxis	Stopcox1 (Swiss HIV Cohort Study), Switzerland	Prospective observational, CD4 > 200 and 14% for at least 12 weeks
Disseminated *M. avium* infection	Primary prophylaxis	ACTG 362, USA	Randomized Trial, CD4 > 100
		CPCRA, USA	Randomized Trial, CD4 > 100
	Maintenance therapy	ACTG 393, USA	Randomized Trial, CD4 > 100, completion of at least one year of effective antimycobacterial therapy
Cytomegalovirus retinitis	Maintenance therapy	RESTIMOP (ANRS 078), France	Prospective observational, CD4 > 75, HIV-RNA > 4.5 log
		ACTG 379, USA	Prospective observational, CD4 > 100 for ≥ 3 months, healed retinitis, ≥ 2 months of anti-CMV therapy
Histoplasmosis	Maintenance therapy	ACTG 5038	Prospective observational, CD4 > 150, completion of at least one year of effective antifungal therapy

important information regarding the effectiveness of such practice.

Conclusions

The feasibility of discontinuing primary prophylaxis and maintenance therapy for various opportunistic infections is an important issue in the current era of successful potent combination antiretroviral therapy. The possibility of successfully stopping medication, often after many months to years of chronic use, may psychologically be of great benefit to patients, increase their quality of life, and lead to a more optimistic perception of living with chronic HIV infection.

While for most OI's, discontinuation may be safe for persons with a sustained significant increase of CD4 cell counts, in a formal sense sufficient data are only available from studies addressing the discontinuation of primary PCP prophylaxis in patients with an increase of CD4 cells to at least 200cells/µL that is sustained for at least 3 months (Table 1).

The criteria for what can be considered an acceptable risk-benefit ratio concerning prophylaxis/maintenance therapy discontinuation optimally need to be defined for all major OI's taking into account the efficacy and safety of currently recommended prophylactic regimens as well as the clinical severity of the respective OI. Acceptable incidence levels should be formulated for *each OI*, based on data concerning the efficacy of current approaches to primary and secondary prophylaxis. These levels can then be used to judge whether the risk of primary or recurrent opportunistic disease is acceptably low in prospective or retrospective studies of prophylaxis/maintenance therapy discontinuation. A summary of ongoing prospective studies is given in Table 2.

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