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Disseminated *Mycobacterium avium-intracellulare* Complex (MAC) Infection in the Era of Effective Antiretroviral Therapy

Is Prophylaxis Still Indicated?

Christoph G. Lange,[1] *Ian J. Woolley*[2] and *Reinhard H. Brodt*[3]

1 Medical Clinic, Research Center Borstel, Borstel, Germany
2 Department of Infectious Diseases and Clinical Epidemiology, Monash Medical Centre, Clayton, Victoria, Australia
3 Department of Internal Medicine, Division of Infectious Diseases, Johann Wolfgang Goethe University, Frankfurt, Germany

Abstract

Before highly active antiretroviral therapies (HAART) were available for the treatment of persons with HIV infection, disseminated *Mycobacterium avium-intracellulare* complex (MAC) infection was one of the most common opportunistic infections that affected people living with AIDS. Routine use of chemoprophylaxis with a macrolide has been advocated in guidelines for the treatment of HIV-infected individuals if they have a circulating CD4+ cell count of ≤50 cells/μL. In addition, lifelong prophylaxis for disease recurrence has been recommended for those with a history of disseminated MAC infection.

The introduction of HAART has resulted in a remarkable decline in the incidence of opportunistic infections and death among persons living with AIDS. Considerable reconstitution of functional immune responses against opportunistic infections can be achieved with HAART. In the case of infection with MAC, there has been a substantial reduction in the incidence of disseminated infections in the HAART era, even in countries where the use of MAC prophylaxis was never widely accepted. Moreover, the clinical picture of MAC infections in patients treated with potent antiretroviral therapies has shifted from a disseminated disease with bacteraemia to a localised infection, presenting most often with lymphadenopathy and osteomyelitis.

Data from several recently conducted randomised, double-blind, placebo-controlled trials led to the current practice of discontinuing primary and secondary prophylaxis against disseminated MAC infections at stable CD4+ cell counts >100 cells/μL. These recommendations are still conservative as primary or secondary disseminated MAC infections are only rarely seen in patients who respond to HAART, despite treatment initiation at very low CD4+ cell counts.

Potential adverse effects of macrolide therapy and drug interactions with antiretrovirals also metabolised via the cytochrome P450 enzyme system must be critically weighed against the marginal benefit that MAC prophylaxis may provide in addition to treatment with HAART. These authors feel that, unless patients who initiate HAART at low CD4+ cell counts do not respond to HIV-treatment,

routine MAC prophylaxis should not be recommended. Nevertheless, the patient population for whom MAC prophylaxis may still be indicated in the era of HAART needs to be identified in prospectively designed clinical trials.

Since the discovery of the HIV in the early 1980s, the HIV pandemic has become a major threat to human life and the economy worldwide. Approximately 40 million people are infected globally, of whom about 3 million die each year.[1] Infections and deaths are expected to continue to increase. HIV causes morbidity and mortality through depletion of CD4+ T cells leading to AIDS, with an average time of infection to clinical disease of around one decade.[2] This progressive loss of immune function results in loss of immune control of latent infections such as tuberculosis, and increased vulnerability to otherwise benign environmental or colonising organisms such as *Pneumocystis jiroveci* (formerly named *Pneumocystis carinii)*. The spectrum of opportunistic infections is quite broad, however, and becomes even broader as immunity wanes. Opportunistic infections seen at high frequency in developed countries include *Pneumocystis* pneumonia (PCP), dissemination of *Mycobacterium avium-intracellulare* complex (MAC), retinal and gastrointestinal cytomegalovirus (CMV) infections, cryptosporidiosis and cerebral toxoplasmosis.[3,4] Infections important in certain geographical locations include histoplasmosis in parts of the US[5] and *Penicillium marneffi* in Thailand.[6]

The pattern of opportunistic infections seen in patients living with HIV is reflected in particular by the progressive impairment of cell-mediated immunity as CD4+ cell counts decrease over time with ongoing viral replication. Progressive immunodeficiency in HIV infection also leads to cell-mediated loss of tumour-controlling immune surveillance, putting affected persons at an increased risk for the development of malignancies, especially those associated with infections such as Kaposi's sarcoma.[7] Even before the introduction of antiretroviral therapies that could effectively suppresses viral replication, prophylactic treatment against the development of some of the opportunistic infections such as PCP, disseminated MAC and cerebral toxoplasmosis reduced the incidence of these infections in HIV-infected patients with a concomitant improvement in lifespan.[8,9] With the introduction of highly active antiretroviral therapies (HAART) that allow for control of viral replication and restoration of antigen-specific immune responses in HIV-infected patients,[10-13] HIV-related morbidity and mortality has decreased dramatically by as much as 80% in countries where these therapies are widely available.[14-16]

Many recommendations on primary prophylaxis against opportunistic infections in AIDS patients still use studies undertaken in the era before HAART.[17,18] Over 7 years after HAART became available, it is still uncertain whether immune reconstitution achieved by potent antiretroviral therapies alone makes prophylaxis against opportunistic infections, even in patients who start HAART at advanced stages of HIV infection, still necessary. Primary prophylaxis against disseminated MAC infection must be critically questioned, as it has never been widely accepted, even in developed countries, partly because the benefits appeared to be small and partly because it was not commonly seen in some regions.[19-21] This review discusses the epidemiology and clinical presentation of MAC infection in patients living with AIDS, mechanisms of MAC-specific immunodeficiency and treatment options, and focuses on the question of whether prophylactic therapy against MAC disease should still be recommended for HIV-infected patients in the era of HAART.

1. *Mycobacterium avium-intracellulare* Complex (MAC)

1.1 History and Clinical Presentation

MAC infection in patients with HIV infection is distinct from what is usually seen in individuals not infected by HIV. In non-immunocompromised adults, what is usually seen is an indolent pulmonary illness and it may be difficult to determine whether the organism is commensal or pathogenic, even in those with underlying lung disease.[22] In children,

MAC often presents with isolated cervical lymphadenopathy and may be cured by an excisional biopsy of the lymph node without further therapy.[22]

Early in the AIDS epidemic a syndrome of systemic MAC infection was described that was previously only seen in patients with cell-mediated immune defects such as hairy cell leukaemia.[23-26] MAC caused an illness characterised by symptoms of fever, night sweats, anorexia, fatigue and wasting, sometimes with diarrhoea or evidence of other focal organ involvement.[27,28] Anaemia, generalised lymphadenopathy and hepatosplenomegaly were often present on examination.[29] MAC was typically seen in those HIV-infected individuals with advanced immunodeficiency, generally with a CD4+ cell count <50 cells/μL.[30,31] Another clue on biochemical testing was often a raised alkaline phosphatase.[29] Patients were usually diagnosed clinically, and the diagnosis confirmed on positive mycobacterial blood cultures. Stool cultures positive for MAC could also be indicative of incipient clinical disease.[32]

Natural history studies suggest MAC infection may still develop in up to 30% of patients with advanced HIV disease,[33,34] and incidence rates may also largely depend on seasonal and geographical variations.[35]

1.2 Treatment for Disseminated MAC

Treatment for HIV-associated MAC infection advanced slowly using a plethora of antimycobacterial medications, including amikacin, clofazimine, ethambutol, isoniazid, rifampicin and rifabutin. In the early to mid 1990s clinical studies documented the advantage of combination therapy using macrolides and ethambutol as a backbone.[36,37] Studies showing benefit with clarithromycin monotherapy were also published,[38,39] followed by randomised, prospective multidrug trials.[40-42] The proportion of patients becoming blood culture negative using the combination of clarithromycin and ethambutol was, respectively, 65[42] and 69%[40] in two studies. The addition of rifabutin to a regimen based on clarithromycin and ethambutol did not increase the proportion of patients becoming blood culture negative (69%) but the three-drug regimen led to a lower relapse rate (68% relapse with the two drugs versus 12% relapse with the three drugs) at 36 weeks.[40] Recently, a multicentred, prospective clinical trial demonstrated a survival benefit for patients receiving a three-drug regimen based on clarithromycin, ethambutol and rifabutin compared with patients who received a two-drug regimen with clarithromycin and either ethambutol or rifabutin.[43] In contrast, the addition of clofazimine to clarithromycin and ethambutol led to a worse outcome.[42]

These trials confirmed the superiority of macrolide therapy in combination with ethambutol, and led to the cessation of use of several other agents, including clofazimine and isoniazid, for this indication. Rifabutin and ciprofloxacin[44] have become the recommended third agents where more than two drugs were felt indicated. However, the concomitant use of rifabutin and clarithromycin has been associated with anterior uveitis.[45] This therapy anticipated the widespread use of protease inhibitor-based HAART in 1996, but resulted in a decrease in recurrent bacteraemia in the order of 70% if a three-drug regimen was used for treatment.[46] Most authorities recommend lifelong therapy for as long as the patient has low CD4+ cell counts.[47]

1.3 Prophylaxis

MAC affected up to half of patients with AIDS in the pro-HAART era and became relatively more important as widespread use of PCP prophylaxis led to a decline in the incidence of that condition.[8,9,18] The initial infection with MAC occurs by inhalation to the lungs or by ingestion via the gastrointestinal tract. MAC was demonstrated to be present in water, cheese and fish, and no intervention aimed at avoidance of exposure consistently worked.[48-52] Subsequently, it became apparent the organism is environmentally ubiquitous, so pharmacological primary prophylaxis became a more important strategy.

Some early studies showed a benefit to prophylaxis with rifabutin at a dosage of 300 mg/day.[53] Although that benefit was in the order of 50% (with an overall incidence in the placebo arm of 17–18%), there were other issues of drug interactions related to the cytochrome P450 system and mycobacterial resistance to rifabutin monotherapy and its wider implication for rifampicin resistance in individuals infected with *Mycobacterium tuberculosis*. Nevertheless, some authorities recommended the routine

use of rifabutin prophylaxis in persons with CD4+ cell counts <100 cells/μL.[54]

Larger randomised, placebo-controlled trials on primary prophylaxis of MAC in HIV infection were published in 1996, just before potent antiretroviral therapies became available. In a large randomised trial patients with a CD4+ cell count of <100 cells/μL received either clarithromycin 500mg twice a day or placebo. The incidence of MAC bacteraemia was decreased from about 16 to 6% by prophylaxis and this was accompanied by a significant increase in survival (hazard ratio 0.75, p = 0.026; i.e. mortality was about 25% greater in the placebo arm, perhaps not solely due to the prevention of MAC but also to decreases in other bacterial infections at 10 months).[55] A similar benefit in preventing MAC infection (24.7 versus 10.6%) was also seen in a study of once-weekly macrolide prophylaxis with azithromycin 1200mg,[56] although there was no statistically significant difference in all-cause mortality. Yet another trial demonstrated the superiority of azithromycin compared with rifabutin for primary prophylaxis.[57] Clinical trials on primary prophylaxis against disseminated MAC infection in the pre-HAART era are summarised in table I. Azithromycin prophylaxis also reduces risk of PCP and bacterial infections in HIV-infected individuals,[56-58] but rapid development of macrolide resistance of colonising facultative pathogenic bacteria of the upper respiratory tract, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*, have been observed in those who receive prophylaxis.[59]

The results of the primary prophylaxis studies have led to the inclusion of macrolide prophylaxis in treatment guidelines as primary prophylaxis at low CD4+ cell counts (e.g. guidelines from the US Public Health Service/Infectious Diseases Society of America[47] and from Australia[62]). Although mathematical models suggested cost effectiveness of preventive treatment against MAC with azithromycin for patients with advanced HIV infection in the US and Europe,[63,64] implementation of primary prophylaxis for disseminated MAC has been problematic in clinical settings. Adherence to therapy plays the key role in the effectiveness of HIV treatment but many HIV infected persons fail to adhere to HAART and prophylaxis against opportunistic infections because of a high daily pill burden and adverse effects of the therapy.[65-69] In one study, 42% of patients reported non-adherence 1 year after they initiated prophylaxis.[70] Thus, instead of increasing the risk of non-adherence and subsequent treatment failure by the additional pill burden of primary prophylaxis against MAC, many patients profit from simplification of treatment regimens and restriction to the essential drugs of HAART for successful therapy.

2. Prophylactic Therapy Against Other Opportunistic Infections

The experience with MAC prophylaxis mirrors that seen with other opportunistic infections.

For primary prophylaxis against PCP, cotrimoxazole (sulfamethoxazole/trimethoprim) at CD4+ cell counts <200 cells/μL is widely recommended and has unquestioned efficacy.[47] There are several trials of cessation of primary and secondary prophylaxis that demonstrate lack of development of PCP in the setting of HAART. These include both observational studies and open, randomised trials.[71-75] In general, it is therefore considered safe to stop prophylaxis now once the CD4+ cell count has been >200 cells/μL for 3 months or more, although rare failures of this strategy occur.[76]

A series of studies have been conducted in other forms of secondary prophylaxis, including CMV,[77-79] cerebral toxoplasmosis,[77,80,81] candidiasis[82] and cryptococcosis,[77,83] resulting in similar recommendations and findings. The current US guidelines now recommend that secondary prophylaxis for PCP can be ceased once CD4+ cell counts have reached >200 cells/μL for 3 months or more, and that they can be ceased for MAC, cryptococcosis, toxoplasmosis and CMV-retinitis after reaching >100–200 cells/μL for 6 months or more depending on the organism and duration of previous therapy.[17]

3. Immunodeficiency in AIDS and Co-infection with MAC

Normally, CD4+ T cells act as the conductors of an orchestrated immune response,[84-86] but in HIV infection they themselves become functionally impaired and numerically depleted as they act as the

Table I. Clinical trials evaluating the efficacy of primary prophylaxis against disseminated *Mycobacterium avium-intracellulare* complex (MAC) infection in patients with HIV infection at times when potent antiretroviral therapies were not yet available

Study	Year	Country/region	No. of patients	CD4+ cell count (cells/μL)	Follow-up (days)	Agent	Dosage (mg/day)	MAC (%)	Hazard ratio	Survival hazard ratio
Nightingale et al.[53]	1993	USA	292	<200	231	Rifabutin	300	8.2		
			298	<200	214	Placebo		17.1	0.43	NS
Nightingale et al.[53]	1993	USA and Canada	274	<200	185	Rifabutin	300	8.8		
			282	<200	190	Placebo		18.1	0.47	NS
Pierce et al.[55]	1996	USA and Europe	333	<100	427	Clarithromycin	500	5.7	0.31	0.75
			334	<100	402	Placebo		15.9		
Havlir et al.[57]	1996	USA	236	<100	296	Rifabutin	300	23.3	AvR 0.53	NS
			233	<100	315	Azithromycin	1200/wk	13.9	A+RvR 0.28	NS
			224	<100	344	Rifabutin + azithromycin	300 + 1200/wk	8.3	A+RvA 0.53	NS
Maslo et al.[60]	1997	France	371	<100	249	Rifabutin	300	4.6	0.41	NS
			198	<100	361	Placebo		11.1		
Oldfield et al.[56]	1998	USA	89	<100	400	Azithromycin	1200/wk	10.6		
			91	<100	340	Placebo		24.7	0.34	NS
Benson et al.[61]	2000	USA	398	<100	574	Rifabutin	300–450	15.0	RvC 0.56	NS
			391	<100	595	Clarithromycin	1000	9.0	R+CvR 0.43	NS
			389	<100	595	Rifabutin + clarithromycin	300–450/1000	7.0	R+CvC 0.79	NS

A = azithromycin; **C** = clarithromycin; **NS** = not significant; **R** = rifabutin; **v** = versus.

Table II. Clinical trials on discontinuing maintenance therapy (secondary prophylaxis) against disseminated *Mycobacterium avium-intracellulare* complex (MAC) infection in patients with HIV infection

Study	Year	Country/region	No. of patients	CD4+ cell count at MAC diagnosis (cells/μL) [median]	CD4+ cell count at therapy interruption (cells/μL) [median]	Events per person-years of follow-up
Kirk et al.[124]	1999	Denmark	66	9	187	0/5.7
Rossi et al.[118]	2001	Switzerland	24	11	127	0/56.6
Shafran et al.[122]	2002	Canada	52	16	230	1/86.6
Kirk et al.[77]	2002	Europe	103	16	190	2/222
Zeller et al.[123]	2002	France	26	10	105	4/100
Aberg et al.[120]	2003	USA	48	Not mentioned	240	1.4/100

host cell for viral replication. Although HIV-specific CD4+ T cells are preferentially targeted by the virus, in chronic HIV infection the majority of viruses replicate in CD4+ T cells specific for antigens unrelated to HIV.[87] Thus, HIV infection is fundamentally characterised by a progressive, polyclonal decrease in CD4+ T-cell number and function that renders those infected vulnerable to the acquisition of opportunistic infections and neoplasms.[88-90]

As advanced immunodeficiency develops MAC-specific T-helper cell functions are also diminished.[91-94] Despite upregulation of proinflammatory cytokines, such as tumour necrosis factor-α and interleukin-6,[95-97] defence mechanisms against MAC, such as the killing of intracellular organisms by macrophages, the killing of infected macrophages by cytotoxic T lymphocytes or granuloma formation, are also severely and progressively impaired.[98] Consequently, there is loss of local control of MAC infection and the potential for its dissemination through the body, via both lymphatic and haematogenous spread.[98-100]

Disseminated MAC infection in HIV infection is almost exclusively seen in patients with advanced immunodeficiency, when circulating CD4+ cell counts fall below 50 cells/μL.[34,101] When MAC infects HIV-infected individuals there is an additional suppression of CD4+ cell function that can be directly attributable to MAC antigen[94] and upregulation of HIV.[102] Furthermore, replication of HIV in MAC-containing macrophages[103] can be observed that may accelerate further T-cell activation and destruction of the immune defence system.

4. Reconstitution of Immune Responses Against MAC on Highly Active Antiretroviral Therapies

With the advent of HAART in recent years, therapeutic suppression of viral replication can be achieved, resulting in significant increases in circulating CD4+ T cells.[10,12,13,104-107] These *in vitro* indices of immune reconstitution are reflected by a dramatic decline in HIV-related morbidity and mortality in places where HAART is available.[14,15,108,109] Although restoration of the immune phenotype and immune function may remain incomplete when HAART is initiated at advanced stages of HIV-1 infection,[110-112] substantial clinical benefits can still be achieved.[113] Following the initiation of HAART, MAC-directed cell-mediated immunity can be rapidly reconstituted even in patients with advanced HIV disease. In a study on the restoration of MAC-specific immune responses, following the introduction of HAART, *in vitro* responsiveness to MAC was detected as early as 3 months after the initiation of antiretroviral therapy and approached levels comparable with uninfected controls after 6 months of treatment.[114] Since the majority of early CD4+ T cell redistribution is attributed to CD45RO+ memory T cells,[10] these antigen-specific helper cell responses are most likely to never be lost, but rather attenuated, even in the later stages of AIDS. Decreases in MAC incidence observed since the introduction of HAART have been attributed to a direct effect of antiretroviral therapies leading to immune reconstitution rather than to increased adherence to prophylaxis, which tends to decline in many areas and only seems to be of additional benefit in regions with high incidence of

MAC, such as the central southern region of the US.[115-118]

5. Discontinuation of Secondary Prophylaxis

As MAC-specific immunity can be partially restored with antiretroviral therapy, lifelong secondary prophylaxis is no longer recommended.[119] Indeed, a series of more recent clinical trials demonstrate secondary prophylaxis against MAC can safely be discontinued in patients with a history of disseminated MAC who respond to HAART and reach sustained CD4+ cell counts >100 cells/μL (table II).[77,118,120-123]

In all of these studies combined, the average incidence rates for MAC after interruption of maintenance therapy was 2.7% (range 0–11%). Not unexpectedly, the relapse rate was highest in the study with the lowest median CD4+ cell count at the time of maintenance therapy interruption (table II). The presenting features of the illnesses seen were not typical of MAC in the pre-HAART era. Of the seven patients who were characterised with MAC relapse after interruption of secondary prophylaxes, three presented with osteomyelitis, one with an abscess and one without apparent clinical illness but a positive cerebrospinal fluid culture for MAC. One of the two additional patients was solely diagnosed by clinical features and only one patient presented with classical with MAC bacteraemia. In contrast with systemic disease, osteomyelitis and lymphadenopathy seem now to be the characteristic presentations of MAC in the era of HAART.[125-128] Of the six patients in the secondary prophylaxis interruption studies with documented CD4+ cell counts at the time of MAC relapse, five had CD4+ cell counts >100 cells/μL (mean 189, range 126–270 cells/μL). Only one patient relapsed with virological failure at a CD4+ cell count <50 cells/μL. The lack of disseminated disease in most of the patients who relapsed, the unusually high CD4+ cell counts in these cases and the *in vitro* evidence on immune reconstitution led to the speculation that MAC disease in these patients occurs primarily in privileged sites at which immune surveillance is limited and where MAC has been able to maintain itself despite reconstitution of the immune system.[120]

6. Discontinuation of Primary Prophylaxis

The beneficial effect of HAART in the reduction of the incidence of MAC has been clearly demonstrated in two large, double-blind, placebo-controlled trials[129,130] and one prospective, multicentre cohort study[20] (table III). These studies examined the question of discontinuation of primary MAC prophylaxis with azithromycin in patients whose CD4+ cell counts had increased from <50 to >100 cells/μL. Of the 1418 patients in these three studies (614 of whom received azithromycin; 804 received placebo or did not take prophylaxis) who were followed for a median of >1 year, only two cases of MAC occurred. Again, these patients, who belonged in a placebo group, presented with MAC osteomyelitis at relatively high CD4+ cell counts of 203 and 306 cells/μL, respectively.

As a result of these clinical studies, it has been recommended to discontinue MAC prophylaxis at sustained CD4+ cell counts >100 cells/μL. Since the incidence of MAC infection after successful responses to HAART is very low, regardless of prophylaxis with azithromycin,[20,117,129,130] and since prophylaxis does not prevent the development of MAC despite HAART,[131] it is unclear whether patients who are treated with HAART benefit from MAC prophylaxis at all. The effect of MAC prophylaxis on the incidence of MAC infection in all patients of a cohort of HIV-infected individuals who initiate HAART at CD4+ cell counts <50 cells/μL has not been investigated prospectively to date. Patients whose CD4+ cell counts remain <50 cells/μL

Table III. Clinical trials on discontinuing primary prophylaxis against disseminated *Mycobacterium avium-intracellulare* complex (MAC) infection in patients with HIV infection

Authors	Year	Country	No. of patients	CD4+ cell count nadir (cells/μL)	CD4+ cell count at study entry (cells/μL)	Events per person-years of follow-up
Furrer et al.[20]	2000	Switzerland	253	10	>100	0/364
Currier et al.[129]	2000	USA	643	<50	226	0.5/100
El-Sadr et al.[130]	2000	USA	520	23	230	0–0.15/100

despite HAART clearly have an ongoing increased risk of opportunistic infections and death[113] and are likely to benefit from MAC prophylaxis. The situation is less clear in patients whose CD4+ cell counts increase above 50 cells/μL but does not reach 100 cells/μL, or who are treated with HAART only for a short period of time. In the Swiss HIV Cohort Study,[132] 21 of 2410 patients who started HAART at a median CD4+ cell count of 16 cells/μL subsequently developed MAC infection, 16 of those within the first 3 months of therapy. The majority of these cases may be attributed to inflammatory responses in the process of immune reconstitution to previously subclinical infection.[126,133,134] A recent study from Canada attributed 23% of MAC infections in the era of HAART to localised lymphadenopathy.[135] These infections also occurred in the first few months after initiation of therapy. Interestingly, while MAC prophylaxis with azithromycin was related to a significant risk reduction (incidence rates 2.7 events/100 person-years versus 8 events/100 person-years) in that study, this protection did not seem to affect immune reconstitution disease and it was only relevant for those patients who were either not taking or not responding to HAART.[135]

In the cohort of the Frankfurt University Hospital HIV clinic in Germany where no patient received primary prophylaxis against MAC infection, 4.4% of patients (36 of 824) who presented with an AIDS-defining illness in the HAART era in the years 1996–2002 had a MAC infection (figure 1) [RH Brodt, unpublished data]. Eleven of those patients initially presented with MAC infection at the time of the HIV diagnosis and six patients where non-adherent to medications. Out of the 19 of 824 patients (2.3%) who may have benefited from a primary MAC prophylaxis, 16 (84%) developed the infection between 4 and 8 weeks after the initiation of HAART and the majority of these cases may again be attributed to immune reconstitution disease.

A prospective, randomised, placebo-controlled trial is needed to address the question of whether primary MAC prophylaxis is still necessary in HIV-infected individuals who initiate treatment with antiretroviral therapies at CD4+ cell counts of <50 cells/μL.

Similarly, it remains to be ascertained whether patients whose CD4+ cell counts drop again to <100 cells/μL, after previous increases in their CD4+ cell counts on therapy, need to restart primary or secondary prophylaxis.

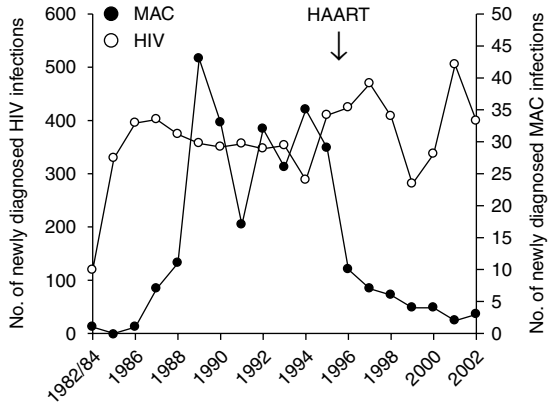

Fig. 1. Numbers of newly diagnosed HIV infections and *Mycobacterium avium-intracellulare* complex (MAC) infections by year (as defined by microbiological diagnosis and clinical symptoms) in the Frankfurt (Germany) HIV clinic cohort between the years 1982 and 2003. The arrow indicates the advent of highly active antiretroviral therapy (HAART) in 1996. No patient in this cohort received primary prophylaxis against disseminated MAC infection.

7. MAC Prophylaxis in Resource Poor Settings

In the pre-HAART era, infection with MAC was the most prevalent bacterial opportunistic infection in patients living with AIDS in developed countries.[101,136] In contrast, disseminated MAC infection has been reported to be relatively uncommon in developing countries, especially sub-Saharan Africa, the area with the highest burden of HIV-infection in the world.[137-140] For example, the annual frequency of disseminated non-tuberculous bacteria-related infections in the Black African population in Cape Town, South Africa, has been estimated to be <1%,[141] although one study from Johannesburg recently reported a point prevalence of 10% for disseminated MAC infection in patients with CD4+ cell counts <100 cells/μL.[142] Lower rates of disseminated MAC infection in patients with AIDS in developing countries have been attributed to less exposure and differences in immunity.[143] It has been speculated that Bacille Calmette Guerin vaccination, which is frequently given at birth in Africa, or latent tuberculosis, which is highly prevalent, may protect against MAC infection.[141] In contrast,

tuberculosis is the most serious HIV-associated infection in developing countries and the most common cause of death in Africans living with AIDS.[144] Under these circumstances, many patients susceptible to mycobacterial infections with AIDS die of tuberculosis and other opportunistic infections before reaching the advanced stage of immunodeficiency that puts them at risk for MAC infection. Lower incidence of MAC infection, lack of identification of patients at risk for MAC infection by laboratory surveillance and limited financial resources have thus far prevented the application of MAC prophylaxis in developing countries.

8. Conclusions

As a result of immune reconstitution, disseminated MAC infections in patients with AIDS have dramatically declined in all countries where antiretroviral therapies are the standard of care for HIV-infected patients, even though primary MAC prophylaxis was not widely accepted in most countries outside of North America. Regional differences in following the guidelines for primary MAC prophylaxis among physicians taking care of HIV-infected patients in the era of HAART are a result of variations of MAC incidence rates, and of diverging opinions about benefits and risk of prescribing a prophylaxis with relatively low efficacy. Randomised clinical trials have shown that it is safe to interrupt primary prophylaxis against disseminated MAC infection at stable CD4+ cell counts >100 cells/μL in patients who started this prophylaxis at advanced stages of AIDS while CD4+ cell counts were <50 cells/μL. However, even guidelines based on these results may be too conservative. There is currently little to support recommending primary prophylaxis against disseminated MAC infection for HIV-infected patients, even for those with CD4+ cell counts <50 cells/μL, unless these patients do not respond or adhere to HAART. In consequence, interruption of primary MAC prophylaxis should be offered to all patients with stable response to HAART. Similarly, secondary prophylaxis for disseminated MAC infection should not be recommended indefinitely for those who respond to HAART but can be offered to be discontinued once stable CD4+ cell counts >100 cells/μL have been reached.

As incidence rates for disseminated MAC infections are very low once HAART has been initiated, clinical trials enrolling large numbers of patients will be needed to show a significant benefit of primary prophylaxis. In recent years, many HIV-infected patients at risk for MAC infections in developed countries have either never received, are intolerant to or do not adhere to HAART and MAC prophylaxis. In certain situations, such as in geographical regions with a high incidence of MAC (e.g. the south central region of the US), primary prophylaxis against disseminated MAC should still be considered in patients with good compliance but without immunological responses to HAART or in patients who undergo treatment interruptions when CD4+ cell counts are very low. Patients who begin HAART at CD4+ cell counts <50 cells/μL should be followed carefully for clinical signs of MAC infection in the first months after treatment initiation. With response to therapy, the risk of disseminated MAC infection thereafter is extremely low and can most probably not be prevented by prophylaxis.

A number of open questions still need to be addressed. For example, are there individual risk factors for recurrence of MAC other than CD4+ cell counts? How long should CD4+ cell counts be above the current consensus threshold of 100 cells/μL before secondary prophylaxis can safely be interrupted and when should secondary prophylaxis be restarted once CD4+ cell counts drop below this level again?

Even in some patients who profit from HAART and secondary prophylaxis, MAC will continue to cause morbidity despite treatment. Physicians treating patients with HIV infections need to be aware that the clinical presentation of MAC infection has shifted from a systemic infection to predominantly localised diseases in those receiving potent antiretroviral therapies.

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Correspondence and offprints: Dr *Christoph G. Lange*, Medical Clinic, Research Center Borstel, Parkallee 35, 23845 Borstel, Germany.
E-mail: clange@fz-borstel.de