

Therapy and prophylaxis of opportunistic infections in HIV-infected patients: a guideline by the German and Austrian AIDS societies (DAIG/ÖAG) (AWMF 055/066)

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Abstract

Introduction There was a growing need for practical guidelines for the most common OIs in Germany and Austria under consideration of the local epidemiological conditions.

Materials and methods The German and Austrian AIDS societies developed these guidelines between March 2010 and November 2011. A structured Medline research was performed for 12 diseases, namely Immune reconstitution inflammatory syndrome, Pneumocystis jiroveci pneumonia, cerebral toxoplasmosis, cytomegalovirus manifestations,

candidiasis, herpes simplex virus infections, varizella zoster virus infections, progressive multifocal leucoencephalopathy, cryptosporidiosis, cryptococcosis, nontuberculosis mycobacteria infections and tuberculosis. Due to the lack of evidence by randomized controlled trials, part of the guidelines reflects expert opinions. The German version was accepted by the German and Austrian AIDS Societies and was previously published by the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF; German Association of the Scientific Medical Societies).

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Conclusion The review presented here is a translation of a short version of the German–Austrian Guidelines of opportunistic infections in HIV patients. These guidelines are well-accepted in a clinical setting in both Germany and Austria. They lead to a similar treatment of a heterogeneous group of patients in these countries.

Keywords Austrian · German · Guidelines · Opportunistic infections · Prophylaxis · Therapy

Introduction

Although opportunistic infections (OIs) in human immunodeficiency virus (HIV)-infected patients have become rare in industrialized countries [1], patients continue to present with advanced HIV disease and HIV-related OIs. Patients (so-called “late presenters”) are often unaware of their HIV infection or have not received antiretroviral treatment. They present at a late stage and when their overall health status is already poor [2]. Diagnosis and therapy of these OIs remain a challenge.

The aim of the recommendations presented here is to develop general and practical guidelines for the treatment and prophylaxis of the most common OIs in Germany

within the framework of local epidemiological conditions. The tables in the different sections of the guidelines represent a summary of the therapeutic guidelines. With regard to diagnosis, the authors refer to the appropriate literature. At the time the guidelines were approved some articles were only available as congress abstracts; if these were published as peer-reviewed article at a later date, the published articles were cited.

The KAAD (Clinical AIDS Working Group Germany) guidelines conform to the international guidelines of the U.S. Centers for Disease Control and Prevention (CDC) (<http://www.cdc.gov/mmwr>) [3] and guidelines formulated by the AWMF (Association of the Scientific Medical Societies in Germany) in the overlapping fields dermatology and neurology (<http://www.uni-duesseldorf.de/AWMF/II/>). Members of other medical societies and the Austrian AIDS Society have also participated and have been consulted (see [Appendix](#)).

Some of the following recommendations go beyond the approved use of drugs. In many cases, data from randomized controlled trials (RCTs) are missing, and evidence is based on practical and clinical experiences not presented in published studies (expert opinion). In addition, we advise always checking interactions and toxicities of the applied drugs as these factors cannot be described in detail within the scope of this guideline.

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For the treatment of bacterial pneumonia, which is similar in HIV-positive and HIV-negative patients, the appropriate guidelines should be referred to.

Antiretroviral therapy and OI treatment

The indication for antiretroviral therapy (ART) in Germany is based on the guidelines by the German and Austrian AIDS Societies (DAIG and ÖAG, respectively). However, general recommendations regarding when to start ART with mostly ART-naïve patients in the setting of an (acute) OI cannot be given.

In the case of candidiasis, herpes virus infections or, for example, cryptosporidiosis, the immediate start of ART is uncomplicated; in the case of progressive multifocal leukoencephalopathy (PML) it is even necessary and recommended. The situation is more difficult in cases of *Pneumocystis jiroveci* pneumonia (PcP), cerebral toxoplasmosis, cytomegalovirus (CMV)-retinitis, tuberculosis (TB), atypical mycobacteriosis, and cryptococcosis. We refer to the corresponding sections of these guidelines.

The recommendations given here represent the consensus of the guideline consensus group. The recommendations referring to medical therapies might involve off-label therapies that have not been officially approved. This is due to the lack of data from RCTs on HIV-infected patients with OI. In such cases, the recommendation often refers to data on HIV-negative persons or personal experience (expert opinion). It should also be noted that drug–drug interactions or toxicities need to be excluded in each single case.

Materials and methods

The KAAD was given the task to develop guidelines for the treatment and prophylaxis of OI by the DAIG in March 2010. The members of the DAIG, ÖAG, and other German medical societies (in total 24 societies represented; see [Appendix](#)) were asked to participate in the consensus process. The members formed small interest groups ($n = 3–10$ members) covering the different chapters of these guidelines. A first version was sent out in March 2010 based on the corresponding chapters of the digital version (<http://www.hivbook.com>). The different groups were free to base their chapters on this proposal after review of the relevant literature or to create new chapters. Via an email system these new chapters were put together until the groups reached a consensus on a final draft. Four weeks before a consensus conference in Cologne on 25 June 2010, these drafts for all 12 chapters were sent out to all members of all groups and to all DAIG members with the request for suggestions for changes. The submitted suggestions for

changes which were received were then sent out to the members prior to the meeting. During the consensus conference all suggestions were discussed and voted on separately. Finally, each single chapter and the whole guideline proposal were voted on separately. There was an agreement of 100 % on the whole proposal between all members of the guideline group.

In a third step the Cologne proposal was sent out via email to all members of the DAIG four weeks prior to a DAIG member assembly in Munich (17 March 2011) for comment. Only minor revisions were asked for. The guidelines were again put to vote during the meeting. During the final vote the guidelines received 36 positive unanimous votes and were agreed on in the current version as the DAIG/KAAD OI guidelines.

The German version (long version) of these guidelines was submitted to the AWMF on 30 August 2011 and was published online on 8 November 2011 (<http://www.awmf.org/leitlinien/detail/ll/055-006.html>). ÖAG approved these guidelines on 9 November 2011.

Results/Guidelines

Immune reconstitution inflammatory syndrome

The immune system is expected to recover following initiation of ART. Some patients, however, show a paradoxical reaction. With widely varying symptoms, this pattern of disease is defined as immune reconstitution disease, immune reconstitution syndrome, or immune reconstitution inflammatory syndrome (IRIS) [4–7]. Different clinical case definitions exist [8, 9], but the preference in the guidelines is for the consensus definition by the International Network for the Study of HIV-associated IRIS (IN-SHI; <http://www.inshi.umn.edu/>):

1. Response to ART by:
 - a. receiving ART and
 - b. virologic response with $>1 \log_{10}$ copies/ml decrease in HIV RNA.
2. Clinical deterioration of an infectious or inflammatory condition temporally related to ART initiation.
3. Symptoms cannot be explained by:
 - a. expected clinical course of a previously recognized and successfully treated infection,
 - b. medication side effect or toxicity,
 - c. treatment failure,
 - d. complete non-adherence.

Manifestations of IRIS are diverse and range from unspecific symptoms, OIs to autoimmune diseases, and malignomas [10].

Regarding OIs, the physician must differentiate between symptomatic relapse of a prior infection (paradoxical IRIS) and infections first appearing on ART (unmasking IRIS). Data on the incidence of IRIS vary widely, ranging between 10 and 23 % of all patients at initiation of an ART [10–13]. A prospective study showed an incidence rate in Germany of 24.8 % [14]. An international meta-analysis showed a total incident rate of 16.1 % for IRIS, with the highest rates for IRIS uveitis, followed by TB, cryptococcal meningitis, PML, and rarer cases of Kaposi's sarcoma or varicella zoster virus (VZV) infections [13]. The greatest risk factor would appear to be a low CD4 T-cell count of <50 cells/ μ l [12, 15].

Management, treatment, and prophylaxis

Patients starting an ART with a CD4 T-cell count of <200 cells/ μ l and especially those who have a high viral load require close monitoring. Patients with <50 CD4 T-cells/ μ l should also be tested for a latent mycobacterial infection (by culture).

A large prospective trial [16] showed no difference for the development of an IRIS when ART was initiated immediately after patients had started an OI therapy (patients with TB were excluded from the trial). In this study, corticosteroids were often given on initiation of ART in a high number of PcP cases, which possibly suppressed some IRIS cases. For TB and cryptococcosis, however, several studies showed an higher incidence of an IRIS when ART was initiated early [17–19].

Corticosteroids are useful in cases of TB-IRIS [20]. Steroid therapy for 2–6 weeks is recommended for cryptococcal-IRIS (increase of intracerebral pressure). The use of non-steroidal anti-inflammatory drugs (NSAIDs) and thalidomide was recommended in some studies, but a general recommendation can not be given for these agents [21].

ART should only be interrupted in very severe cases. Results of the Swiss HIV Cohort Study prove that consequent isoniazid (INH)-prophylaxis in HIV patients with latent TB significantly reduces the risk of a relapse [22].

In general, prognosis for an IRIS is good and the mortality rate is not higher than that for patients without an IRIS [23].

Pneumocystis jiroveci pneumonia

Pneumocystis jiroveci pneumonia is the most frequent OI in Germany and appears predominantly in HIV-infected patients with advanced immunodeficiency (CD4 T cells <200/ μ l). If there clinical–radiological findings suggest PcP, therapy should be initiated immediately without awaiting results of a bronchoalveolar lavage. A mild PcP

[BGA: partial pressure of oxygen (PO_2) > 70–80 mmHg] can be treated in outpatient medical care. If ventilation becomes necessary, non-invasive methods (continuous positive airway pressure) are beneficial if applied at an early stage [24]. With respect to the treatment of ART-naïve patients, several experts believe that the initiation of ART can be delayed until acute treatment is completed. However, one RCT has shown advantages of an early start [16].

Treatment

Acute therapy should be given at least for 21 days, if necessary longer. The treatment of choice is a combination of trimethoprim and sulfamethoxazole (TMP/SMX, cotrimoxazole). Oral application of TMP/SMX is only recommended in mild cases, but this therapy can be also considered after initial improvement during intravenous therapy. Positive effects with lower doses of TMP/SMX have been observed in some case reports, but data from controlled trials are missing [25]. All severe cases should be treated intravenously in hospital. In cases of respiratory insufficiency [PO_2 < 70 mmHg or alveolar–arterial oxygen tension difference ($AaDO_2$) \geq 35 mmHg on room air], most experts recommend (5)–10 days of adjuvant administration of prednisolone [approx. 1 mg/kg body weight as a single dose or split dose twice daily (bid)]. With prednisolone, mortality risk of severe PcP can be reduced by half and significantly fewer patients require mechanical ventilation [26].

Compared to TMP/SMX, all alternative therapies are less effective. In the event of intolerance or sulfonamide allergy, intravenous pentamidine (4 mg/kg once daily (qd) for 14–21 days is recommended as a second choice; this agent is however more toxic and the dose may therefore have to be reduced after 5 days (2 mg/kg).

Treatment with inhaled pentamidine can be attempted in mild cases of PcP [27, 28]; however, reports on experience with this approach are conflicting [29–31]. Instead of pentamidine, the administration of atovaquone suspension or a combination of trimethoprim and dapsone or clindamycin and primaquine is possible [test for glucose-6-phosphate dehydrogenase (G6PD) deficiency!]. Data are only available for mild to moderate PcP [32–34].

Primaquine is no longer approved for use in Germany, but it is available through international pharmacies. It can only be applied if there are no other alternatives and requires increased efforts in educating patients. According to a meta-analysis, the combination of clindamycin plus primaquine is the most successful therapy if cotrimoxazole therapy fails [35]; this combination appears to be more effective than pentamidine alone [36].

Prophylaxis

Patients with <200 CD4 T-cells/ μ l (or <14 % of total lymphocytic count) or a previous PcP require prophylaxis. The therapy of choice is TMP/SMX, which also has a protective effect against bacterial infections and cerebral toxoplasmosis [37, 38]. Daily administration is possibly more effective than three doses a week [39]. In cases of moderate cutaneous allergic reactions, desensitization is possible [40]. Monthly pentamidine inhalations are a well-tolerated alternative [41, 42]. A suitable inhalation system should be chosen and an inhalative β -sympathomimetic should be administered beforehand. Other options are dapsone [41, 42] and atovaquone, both of which have proved to be similarly effective as TMP/SMX, dapsone, and pentamidine in two multi-center trials [43–45]. Atovaquone, however, proved inferior to TMP/SMX in another study [32].

PcP prophylaxis can be discontinued after successful immune reconstitution on ART to ≥ 200 CD4 T-cells/ μ l for at least 3 months [46–49]. Only a few cases of reoccurring PcP have been reported for discontinuation at >200 CD4 T-cells/ μ l [50, 51]. If the HIV RNA is well suppressed, >100 CD4 T-cells/ μ l may be sufficient to discontinue prophylaxis [52]. However, larger trials would be needed to submit a general recommendation regarding discontinuation for these patients.

The recommendations concerning therapy and prophylaxis of PcP are summarized in Table 1.

Cerebral toxoplasmosis

The incidence of cerebral toxoplasmosis has decreased to less than a quarter of that during the earlier years of the HIV epidemic, [53]. Nevertheless, it remains the most important neurological OI in HIV-infected patients in Europe [54]. Cerebral toxoplasmosis almost always results from a reactivation of a latent infection with *Toxoplasma gondii*. Extracerebral manifestations are rare.

Treatment

Standard therapy is a combination of pyrimethamine and sulfadiazine, which is effective in 75–89 % of cases [55, 56]. An equivalent alternative is pyrimethamine and clindamycin [55, 57]. TMP/SMX is also possible, with the same doses as used in PcP [58, 59]. TMP/SMX proved to be as effective as sulfadiazine/pyrimethamine in two RCTs on ocular and cerebral toxoplasmosis [60, 61]. A Cochrane review showed no superiority of any one specific regimen [62].

For pyrimethamine, a “loading dose” within the first few days has been used since the first studies [56]. However, the efficacy of this approach has not been proven.

Table 1 Therapy and prophylaxis of *Pneumocystis jiroveci* pneumonia^a

Therapy/prophylaxis	Drug	Therapeutic regimen
Acute therapy		Duration: at least 21 days
First choice with moderate/severe PcP	TMP/SMX	TMP 15–20 mg per kg/day (+SMX 75–100 mg per kg/day) applied in 3–4 daily doses (4×2 g or $3 \times 2,5$ g i.v.) Prednisone 50–100 mg (approx. 1 mg/kg for 5–10 days), e.g. 3 days 80 mg, 3 days 40 mg, 3 days 20 mg
Mild PcP	TMP/SMX	3×3 tbl. à 960 mg p.o.
Alternatives	Pentamidine	4 mg/kg i.v. 5 days, then reduction if necessary to 2 mg/kg (blood sugar controls!)
	Atovaquone	2×750 mg (5 ml) suspension p.o. with food
	Clindamycin + Primaquine	(3–)4 \times 600 mg i.v. or p.o. + primaquine 30 mg p.o. qd
	Dapsone ^b + Trimethoprim	Dapsone 1×100 mg qd, trimethoprim 5 mg/kg $3 \times$ daily
Prophylaxis	<200 CD4 T-cells/ μ l, preceding PCP episode	
	Prophylaxis can be discontinued after successful immune reconstitution to ≥ 200 CD4 T-cells/ μ l for at least 3 months	
First choice	TMP/SMX	1×480 mg p.o. qd or 960 mg p.o. $3 \times$ /week
Alternatives	Pentamidine	300 mg $1\text{--}2 \times$ /month via inhalation
	Dapsone	1×100 mg p.o. qd
	Dapsone + Pyrimethamine	1×50 mg qd plus pyrimethamine 1×50 mg/week + folic acid 1×30 mg/week
	Atovaquone	2×750 mg p.o.

PcP *Pneumocystis jiroveci* pneumonia, TMP/SMX trimethoprim and sulfamethoxazole, i.v. intravenous, p.o. oral, od once daily

^a Unless specified otherwise, daily doses; duration of therapy usually at least 21 days

^b Control of glucose-6-phosphate dehydrogenase (G6PDH) regulation with dapsone therapy is recommended

Due to the myelotoxicity of pyrimethamine, it is important to add folinic acid (not folic acid) from the start [63].

Other alternatives are atovaquone/pyrimethamine [64] or azithromycin/pyrimethamine [65]; however, data are limited.

Acute therapy lasts for a period of at least 4 (to 6) weeks—longer for alternative therapies. In most cases, empiric treatment of toxoplasmosis is initiated upon identification by radiographic testing. Any improvement or clinical deterioration should be evaluated clinically and by magnetic resonance imaging (MRI) scanning during therapy (after 14 days). In the case of progression, an alternative diagnosis (i.e., cerebral lymphoma, tuberculoma) and a brain biopsy should be considered.

Maintenance therapy with a reduced dosage should be initiated when lesions have resolved at least by 50 %, the clinical course has improved, and contrast enhancement has been reduced or eliminated.

ART should be initiated as soon as possible. In cases of increased intracranial pressure or extensive edema, steroids can be given (dexamethasone, 3–4 × 4–8 mg/day). The choice for steroid therapy must be considered carefully as steroids distort possible differential diagnoses. For example, primary cerebral lymphomas also respond to steroids, and in the case of therapeutic failure, the validity of a potential biopsy can be reduced with steroids.

Antiepileptic therapy is indicated if epileptic attacks occur. Due to rare interactions with ART, gabapentin, pregabalin, and levetiracetam are applied. Levetiracetam is also available as infusion.

Prophylaxis

A distinction must be made between exposure prophylaxis, primary prophylaxis, and secondary prophylaxis after cerebral toxoplasmosis.

- Exposure prophylaxis: Immunoglobulin G (IgG)-negative patients should avoid eating raw or undercooked meat. An increased risk due to proximity to cats has not been proven [66]. Stricter measures of hygiene should be followed. However, the importance of this recommendation under effective ART is questionable.
- Primary prophylaxis: IgG-positive patients with <100 CD4 T-cells/μl require primary prophylaxis. The drug regimen of choice is TMP/SMX. In cases of allergy, desensitization may be considered [40]. See above for alternatives. Primary prophylaxis can be discontinued if CD4 T-cell count is >200 cells/μl for at least 3 months.
- Secondary prophylaxis: In the absence of immune reconstitution, patients require lifelong secondary prophylaxis, usually consisting of half the dose needed for acute therapy [67]. Clindamycin is presumably less

suitable as secondary prophylaxis as it cannot cross the intact blood–brain barrier [63]. TMP/SMX also seems less effective for secondary prophylaxis. However, it may be considered because it is simple. A higher dose than that for PcP is definitely required [68, 69]. Prophylaxis may be discontinued safely if initial therapy has led to radiological resolution and if there is an immune reconstitution of >200 CD4 T-cells/μl for at least 3–6 months [31, 70–72].

The recommendations on therapy and prophylaxis of cerebral toxoplasmosis are summarized in Table 2.

Cytomegalovirus manifestations

In Germany, seroprevalence of CMV infection in the adult population is 50–70 %. The risk of a reactivation of CMV infection increases when the CD4 T-cell count is <100 cells/μl. In addition to CMV retinitis, impairment of other end-organs may occur. Due to the limited data on CMV manifestations, the same systemic therapy is recommended in these latter cases as for CMV retinitis [73]. International guidelines are also available for this approach [3].

Treatment

All patients with manifest CMV infection should start ART immediately. The CMV-specific immune response is restored [74], leading to a reduction of CMV viremia [75] and delaying progression of an existing CMV retinitis or its recurrence [76, 77]. In addition to ART, a CMV-specific therapy should be initiated at the time of diagnosis.

Therapy of CMV retinitis can be performed locally or systemically. A local therapy alone does not provide protection against dissemination of infection in the contralateral eye or other organs, but it can be considered if systemic drug toxicity is high. For systemic therapy, four substances are available: gancyclovir, foscarnet, cidofovir, and valgancyclovir (ValGCV). The reader is referred to the product information on these substances for the respective side effects.

Valgancyclovir is the only drug that can be administered orally. It is almost completely hydrolyzed to gancyclovir after resorption in the gastrointestinal tract [78, 79]. Gancyclovir and foscarnet are both recommended as first choices for treating CMV retinitis even though foscarnet proved to be superior in pre-ART times [80, 81]. The side effects of both drugs differ, but the response rates to therapy are similar with both substances [81–83]. As foscarnet must be administered via a central catheter, the administration of gancyclovir is easier and often preferred.

Valgancyclovir has proven to be effective in a comparative study and has the advantage of being less

Table 2 Therapy and prophylaxis of cerebral toxoplasmosis^a

Therapy/ prophylaxis	Drug	Therapeutic regimen
Acute therapy		Duration: at least 4 weeks
First choice	Sulfadiazine ^b + Pyrimethamine	4 × 1–1.5 g p.o. + 2 × 50 mg p.o. (for 3 days, then 50–75 mg/d) + folic acid 15 mg p.o.
First choice	Clindamycin + Pyrimethamine	4 × 600 mg i.v. (or p.o.) + 2 × 50 mg (for 3 days, then 50–75 mg/day) + folic acid 15 mg p.o.
Alternative	TMP/SMX	15 mg of TMP component/kg/d, in 3–4 doses a day
	Atovaquone + Pyrimethamine	2 × 1,500 mg p.o. (with food) + 2 × 50 mg p.o. (for 3 days, then 50–75 mg qd) plus folic acid 15 mg p.o. (CDC: loading dose 200 mg, followed by 75 mg/day)
	Depending on findings additional dexamethasone therapy	3–4 × 4–8 mg/day
Maintenance therapy/secondary prophylaxis		
Possible	As for acute therapy	As for acute therapy, but halve dose Discontinue if >200 CD4 T-cells/μl >6 months (if MRI is normal or without contrast enhancement)
	TMP/SMX	1 × 960 mg p.o.
Alternative	Dapsone + Pyrimethamine	50 mg p.o. qd + 50 mg p.o. qd + folic acid 15 mg p.o.
Primary prophylaxis (necessary only if Toxo IgG is positive)		
First choice	TMP/SMX	1 × 480 mg p.o. or 960 mg p.o. 3×/week
Alternative	Dapsone	1 × 100 mg p.o. qd
Alternative	Dapsone + Pyrimethamine	1 × 50 mg p.o. qd + 1 × 50 mg/week + folic acid 1 × 30 mg/week

Toxo IgG Toxoplasma immunoglobulin G, *MRI* magnetic resonance imaging, *CDC* Centers for Disease Control and Prevention

^a Unless otherwise specified, daily doses

^b Cave: acute renal failure due to crystalluria syndrome! Increase fluid intake

complicated to administer than intravenous infusion. Intravenous treatment, however, may be necessary if foveal infections occur with acute risk of impairing visual acuity. In these cases, gancyclovir and foscarnet are equally recommended for first-line therapy. Treatment with both agents consists of an induction therapy followed by life-long maintenance therapy. Induction therapy usually lasts for at least 2–3 weeks until lesions resolve. Without sufficient ART, selection of resistant CMV mutations is frequent and accumulates as the infection progresses [84, 85].

Several authors recommend ValGCV for first-line therapy based on the results of a prospective randomized trial with ValGCV and parenteral gancyclovir [86] and on those of studies on the pharmacokinetics of gancyclovir, with both showing similar results after the administration of ValGCV [78, 79, 86]. Other studies on the pharmacokinetics of gancyclovir following the administration of valgancyclovir either lack a comparison with parenteral gancyclovir [78], or the administered doses were too low to show bioequivalence of ValGCV and gancyclovir [79]. In summary, a clear recommendation in favor of ValGCV cannot be given at the present time. In the presence of sight-threatening lesions, the panel strongly recommends

against treatment with valgancyclovir due to the lack of clear evidence.

Some experts recommend a combination therapy of gancyclovir and foscarnet in full doses for acute sight-threatening lesions. Maintenance therapy with ValGCV can be initiated after lesions have completely resolved [87]; however, this recommendation also lacks data. Without sufficient ART, a relapse is likely to occur, even under maintenance therapy with valgancyclovir.

If lesions (zone II and III) are more anterior, therapy with ValGCV may be attempted with weekly monitoring of the fundus.

Cidofovir has not been tested in controlled trials against gancyclovir or foscarnet. Compared to a delayed therapy, cidofovir significantly slows down the progression of the infection [88]; however, cidofovir is not recommended as first-line therapy due to its side effects. It does remain an important agent in the treatment of progredient CMV retinitis under gancyclovir or foscarnet therapy.

Treatment of recurrences and progression during therapy:

Sufficient ART is crucial for a successful therapy of CMV retinitis. Patients with progredient CMV retinitis on a

gancyclovir regimen can be treated successfully with foscarnet or a combination of foscarnet and gancyclovir [89]. A good response is obtained in many cases with treatment with cidofovir, and this drug can therefore be an alternative.

If foscarnet should fail, gancyclovir or a combination of gancyclovir and foscarnet can be effective. Here too, therapy with cidofovir can prevent further progression. Gancyclovir implants can still be effective after therapy failure under systemic gancyclovir or foscarnet due to the significantly higher intraocular gancyclovir concentration produced by the implants [90]. However, there is no protection against further spread of the infection to other organs or to the contralateral eye [91–93].

Extraocular manifestations

Extraocular manifestations are always treated in the same way as a CMV retinitis, although only a few studies support this recommendation. In the presence of a CMV encephalitis or ventriculitis, clinical experience and smaller case studies indicate that a combination therapy with gancyclovir and foscarnet is superior to monotherapy [94–99]. Due to the toxicity of this therapy, the diagnosis should be confirmed.

Prophylaxis

- Primary prophylaxis: Gancyclovir prophylaxis for CMV retinitis with a CD4 T-cell count of <50 cells/ μ l is effective, but this is usually too toxic. Fundoscopy every 3 months is recommended but not necessary in the opinion of most experts (especially at a CD4 T-cell count of >100 cells/ μ l).
- A dose-reduced secondary prophylaxis should be initiated, preferably with oral ValGCV after about 3 weeks of acute therapy and after lesions have formed scars [87]. Discontinuation of secondary prophylaxis to avoid side effects as soon as possible is recommended and feasible [77, 100, 101]—however, not before at least 6 months of maintenance therapy and immune reconstitution at a CD4 T-cell count of >100–150 cells/ μ l. A small study showed that discontinuation after 18 months of ART/maintenance therapy is already safe at a CD4 T-cell count of >75/ μ l [101]. In the first stage after discontinuation, patients undergo an ophthalmology control at least once a month. The required duration of a recurrence prophylaxis is not clear, nor is it as yet known for how long recurrences with other organ manifestations should be monitored. Duration should therefore be handled as for CMV retinitis.

The recommendations on therapy and prophylaxis of CMV manifestations are summarized in Table 3.

Table 3 Therapy and prophylaxis for cytomegalovirus manifestations^a

Therapy/ prophylaxis	Drug	Therapeutic regimen
Acute therapy		
First choice	Gancyclovir	Duration: at least 3 weeks 2 × 5 mg/kg i.v.
First choice	Foscarnet	2 × 90 mg/kg i.v.
Alternatives	Valgancyclovir	2 × 900 mg p.o.
	Gancyclovir + Foscarnet	2 × 5 mg/kg i.v. 2 × 90 mg/kg i.v.
Maintenance therapy (discontinue when CD4 T-cell count is >100–150/ μ l for >6 months)		
First choice	Valgancyclovir	2 × 450 mg p.o.
Alternatives	Foscarnet	1 × 120 mg/kg i.v. on 5 days/ week
	Cidofovir	1 × 5 mg/kg i.v. every 2 weeks (plus Probenecid)
	Gancyclovir	3 × 10 mg/kg i.v. on 3 days/ week 1 × 5 mg/kg i.v. on 5 days/week
Primary prophylaxis		Not recommended

^a Unless specified otherwise, daily doses

Candidiasis

From the roughly 200 *Candida* species only about 15 different species are encountered in clinical daily practice. The most frequent species by far is *C. albicans*. Clinical response to fluconazole of infections caused by *C. albicans* and *Candida parapsilosis* is mostly good, whereas that to infections caused by *C. glabrata* or *C. krusei* is poor or totally missing. Primary in vitro resistance of *C. albicans* to azoles is rare [102]. Secondary resistance development under long-term azole therapy (fluconazole) was frequently observed in the pre-highly active ART (HAART) era. For the treatment of oral and vulvovaginal candidiasis, the reader is referred to the respective AWMF guidelines [103, 104]. Esophageal candidiasis (thrush) does not require an endoscopy to confirm the diagnosis in the presence of a typical clinical course and a mouth sore.

Treatment

The imidazole antimycotics, such as clotrimazole and the hydroxypyridone ciclopirox olamine, are suitable for local therapy of cutaneous candidiasis. If the immune status of the patient is good and/or in the case of a first episode of an oral candidiasis (OC), topical antimycotics, such as suspensions or pastilles (nystatin, amphotericin B, miconazole), are more inexpensive therapy options, although inferior to a therapy with fluconazole [105–107]. However, adherence is restricted with topically effective

suspensions/pastilles. Alternatives are mucoadhesive applications, although these are clearly more expensive. Oral therapy with systemical azole derivatives (fluconazole, itraconazole, posaconazole, voriconazole) show a more rapid response, provide longer protection against recurrences, and are tolerated better by patients [108–111].

Fluconazole can be considered the drug of choice for OC and esophageal candidiasis. A once-daily oral therapy (100 mg for 5–14 days) has been established as the standard for OC [112]. Single doses of up to 750 mg fluconazole have been tested in a small patient group (mostly without ART) and was considered to be equivalent to a 14-day therapy. This therapy, however, should be confined to patients with compliance problems, as data on late relapses are limited [113, 114].

Esophageal candidiasis is usually treated for 10–14 days with doses of 200–400 mg fluconazole qd. Patients presenting with severe dysphagia can initially be treated intravenously and switched to oral application as symptoms improve. If fluconazole resistance has been detected, treatment with other azole derivatives is usually still effective and should be attempted before parenteral therapy is initiated (e.g., with echinocandin). Traconazole, voriconazole, and posaconazole have demonstrated clinical efficacy for cases of fluconazole refractory oropharyngeal and esophageal candidiasis [115–118]. All azole derivatives require a double dose on the first day of the regimen (loading dose).

Therapy with a higher dose of fluconazole (≤ 800 mg/day ≈ 12 mg/kg/day) or an antimycotic combination therapy [119] can be considered, but data are insufficient. Therapy failure and/or fast relapses occur most frequently in patients with poor immune status (<100 CD4 T-cells/ μ l).

Data from randomized studies have shown that echinocandins (caspofungin, micafungin or anidulafungin) are as effective and well tolerated as fluconazole for the treatment of candida esophagitis [120–122]. However, application should be restricted to azole refractory infections with clear fluconazole resistance [120, 123, 124].

ART should be initiated immediately if chronic recurring oropharyngeal/esophageal candidiasis is present and at the latest if resistance problems occur. Azole refractory candidiasis as well as azole-resistant strains can disappear with sufficient immune reconstitution as a consequence of ART [125, 126].

Prophylaxis

Regular change of toothbrush and thorough cleaning of dentures are a basic recurrence prophylaxis for OC. OC in HIV-infected children and adults can be treated and relapses prevented by applying disinfecting mouth rinses containing chlorhexidine 0.12 % 1–2 \times daily for a 90-day

period [127, 128]. In the pre-HAART era, secondary prophylaxis or life-long therapy with fluconazole led to significant reductions of chronic recurring oropharyngeal candidiasis—but it has also led to the development of secondary resistance [129, 130].

In a randomized study comparing secondary prophylaxis after OC with intermittent therapy on OC recurrence, relapses and infections of systemic candidiasis were reduced by the long-term prophylaxis. However, no survival benefit has been demonstrated for any candidiasis prophylaxis [131]. Primary prophylaxis is not recommended, and indications for secondary prophylaxis should be restricted to individual case.

Table 4 Therapy and prophylaxis for candidiasis^a

Therapy/prophylaxis	Drug	Therapeutic regimen
Acute therapy		
First choice	Fluconazole	200 mg ^b /100 mg 1 \times /day p.o. for oral candidiasis (topical therapy only in very mild cases) for 5–14 days
		1 \times 200 (–400) mg p.o. for esophageal candidiasis (twice the dose on the first day in each case) for 10–14 days
		If Fluconazole not tolerated p.o., it might be given i.v.
Alternatives (in moderate cases)	Amphotericin	Suspension 4 \times 1 ml (100 mg) up to 48 h after symptoms resolve
	Nystatin	4 \times 1 ml (100,000 I.E.) up to 48 h after symptoms resolve
Alternatives in case of fluconazole intolerance	Itraconazole	400 mg loading days 1–3 ^b /then 100–200 mg 2 \times /day p.o. (only as suspension due to poor bio-availability of capsules)
	Posaconazole	400 mg 2 \times /day p.o. (suspension)
	Voriconazole	400 mg ^b /200 mg 2 \times /day p.o.
Alternatives for Azole failure	Anidulafungin	200 mg ^b /100 mg 1 \times /day i.v.
	Caspofungin	70 mg ^b /50 mg 1 \times /day i.v.
	Micafungin	150 mg 1 \times /day i.v.
Prophylaxis		
Primary prophylaxis	Not recommended	
Secondary prophylaxis	In individual cases, generally not recommended	
	Amphotericin	Suspension 4 \times 1 ml/day p.o. (100 mg)
	Fluconazole	If necessary 50 mg every 48 h or 150 mg 1 \times /week

^a Daily doses

^b Keep in mind the loading dose on the first day; with itraconazole for at least 3 days

The recommendations on therapy and prophylaxis of candidiasis are summarized in Table 4.

Herpes simplex infections

Herpes simplex virus (HSV) infections are frequent in HIV-infected patients. Chronic and atypical courses are possible especially in the setting of severe immune deficiency (<100 CD4 T-cells/ μ l). Organs such as the esophagus, central nervous system (CNS), eyes, and respiratory tract may also be affected. In these cases and with persistence of lesions for a period of >4 weeks, HSV infection is an AIDS-defining illness.

Treatment

Topical treatment with acyclovir is adequate for patients with a good immune status and only discrete oral lesions. Penciclovir cream is probably as effective [132]. Genital herpes lesions do not respond as well to topical treatment.

For systemic treatment against HSV-1 and HSV-2, the drug of choice is still acyclovir. Resistance is rare [133], and healing of lesions can be accelerated by the therapy [134]. Severe cases with organ involvement should be treated intravenously. As HSV levels are lower in the CNS than in plasma, the dose to treat encephalitis should be increased. Valacyclovir (ValACV) and famcyclovir are equally effective alternatives to acyclovir [135, 136]. However, they are not approved for patients with immune deficiency and should only be applied if response to acyclovir fails [137].

For uncomplicated genital herpes lesions, shorter regimens of 2 days of 500 mg famcyclovir may be as effective, provided there is no immune deficiency [138].

According to the opinion of some experts, brivudine is an alternative for HSV-1 and VZV, although contraindicated for immunosuppressed patients and only approved for the treatment of VZV. However, results from controlled studies with HIV-infected patients are not available.

In cases of painful mucocutaneous lesions, a local anesthetic can also be applied. Treatment with foscarnet for several weeks may be helpful in exceptional cases, especially if lesions remain refractory to standard treatment [139].

Prophylaxis

Primary prophylaxis is not recommended. An earlier meta-analysis in which acyclovir was found to reduce the risk of both HSV and VZV disease by more than 70 % [140] must be viewed in the context of ART today. Nevertheless, long-term treatment with low-dose acyclovir or ValACV can still be effective treatments for recurrent

HSV [141, 142]. The risk of HIV transmission, which is increased threefold by genital HSV-infection [143], is not reduced by treatment with acyclovir [144–146]. Between 70 and 90 % of patients with symptomatic HSV-2 infection and at least 20–50 % of patients with symptomatic HSV-1 infection experience recurring episodes within the first year. Possible causes are local trauma, UV exposure, fever, and immune suppression. A long-term prophylaxis for at least 6 months is recommended for frequent recurrences. This prophylaxis can prevent further episodes in 70–80 % of cases.

The recommendations on therapy and prophylaxis of genital HSV infections are summarized in Table 5.

Varicella zoster infections

Patients infected with HIV are at increased risk for VZV infection. Multisegmental zoster or zoster generalisatus are often observed with low CD4 T-cell counts. Chronic courses with ulcerating forms and involvement of other organs are rare. Pneumonia or CNS involvement should be considered.

Treatment

A monosegmental zoster can be treated with oral acyclovir. Famcyclovir and ValACV are alternatives. Each complicated, multisegmental or facial zoster should be treated intravenously for 10–14 days. After clinical improvement is evident, a switch to oral therapy is possible.

Zoster neuralgia occurs less frequently in HIV-negative patients treated with the alternative drugs ValACV, famcyclovir, and brivudine than when treated with acyclovir

Table 5 Therapy and prophylaxis of genital Herpes simplex virus infections^a

Therapy/prophylaxis	Drug	Therapeutic regimen
Acute therapy (duration: 7–10 days), daily doses		
First choice	Acyclovir	(3–) 5 × 400 mg p.o.
Severe cases		3 × 5–10 mg/kg i.v. 5 × 800 mg p.o.
Alternatives	Valacyclovir	2–3 × 1,000 mg or 3 × 500–1,000 mg (expert opinion)
Therapy for recurrent Herpes simplex infection virus episodes	Acyclovir	3 × 400 mg p.o. for 5–10 days
	Valacyclovir	2 × 1,000 mg for 5–10 days
	Famciclovir	2 × 500 mg for 5–10 days
Long-term prophylaxis (duration: at least 90 days)	Acyclovir	2–3 × 400–800 mg
	Valacyclovir	2 × 500 mg
	Famciclovir	2 × 500 mg

^a Daily doses

[147]. However, according to a Cochrane analysis, the results of this study are not clear [148]. Brivudine is not licensed for the treatment of immunocompromised patients. Acyclovir resistance is rare and most frequently observed under long-term therapy [149, 150]; in these cases, foscarnet (3 × 40 mg/kg) or cidofovir (5 mg/kg, maximum 375 mg 1×/week) can be given.

Early concomitant and monitored pain management with NSAIDs and/or other opiates in combination with amitriptyline and/or pregabalin is important. For further information on zoster pain, the reader is referred to the AWMF guidelines.

Prophylaxis

Varicella vaccination seems to be fairly safe and effective for patients with a CD4 T-cell count of >400/μl [149]. Vaccination should be considered if VZV serology is negative. In individuals with negative serology and exposure to VZV, administration of hyperimmunoglobulin may be attempted. Long-term primary prophylaxis is usually not effective; however, a long-term low-dose therapy can be considered in the presence of persistent recurring episodes.

The recommendations on therapy and prophylaxis of VZV-infections are summarized in Table 6.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the CNS caused by the John Cunningham virus (JCV). Prognosis for PML was poor in the pre-HAART era, with the median interval between the onset of the first symptoms and death being 3–6 months. With effective ART, there are significantly fewer cases of disease progression, and even complete remission seems possible [151]. Nevertheless, mortality of patients with PML remains high at 50 %, albeit ART [152].

Table 6 Therapy and prophylaxis of varicella zoster virus infection

Therapy/prophylaxis	Drug	Therapeutic regimen
Acute therapy (duration: at least 7 days)		
First choice	Acyclovir	5 × 800 mg p.o.
First choice	Valacyclovir	3 × 1,000 mg p.o.
Alternatives	Famcyclovir	3 × 500 mg p.o.
	Brivudine ^b	1 × 125 mg p.o.
Severe cases	Acyclovir	3 × 10–15 mg/kg i.v.
Prophylaxis		Not recommended

Daily doses

^b Brivudine is not licensed for treatment of immunosuppressed patients and should only be administered in individual cases after weighing up the risks carefully until data from clinical studies are available

Treatment

There is no specific PML treatment with proven efficacy; consequently, the mainstay of therapy is immune reconstitution. As such, priority remains on the initiation and optimization of an ART. Treating physicians are recommended to apply intracerebral penetrating agents. A successful immune reconstitution accounts for a significant reduction in mortality [151–156].

After initiation of ART, a paradoxical worsening of clinical symptoms in terms of an immune reconstitution inflammatory syndrome (IRIS) has been observed in approximately 16–23 % of PML cases. Administration of corticosteroids for PML-IRIS has only been described in case studies [157], and evidence of a benefit was not provided. Given the slight difference in the 1-year survival rate for PML patients and PML-IRIS patients [158], the use of corticosteroids or a temporary discontinuation of ART must be weighed up against the risks of a possible decline of the JCV-specific immune response.

Several supportive immunomodulatory approaches have been tested, but to date there is no convincing evidence for the efficacy of treatments with immunoglobulin, interleukin-2 (IL-2), or IL-α [159]. Therapeutic regimens aimed at inhibiting JCV replication have also been attempted, but as yet relevant evidence supporting the clinical use of drugs such as cytosine arabinoside is not available [153, 160].

Antiviral treatment with acyclovir, cidofovir, ganciclovir, brivudin, ribavirin, foscarnet and the combination therapy foscarnet and zidovudine have also proven to be ineffective [161].

Recently, 5-HT_{2a} inhibitors and/or serotonin receptor antagonists have been discussed for PML treatment. In vitro data for the suppression of JCV replicates via 5HT(2A)R inhibitors are contradictory [162–167]. Results from controlled clinical studies are missing. Based on promising in vitro data [168] a phase I/II study of mefloquine was initiated—only be stopped due to a lack of efficacy. In summary, specific treatments for PML cannot be recommended outside clinical trials.

Prophylaxis

There is no prophylaxis. Exposure prophylaxis is also not possible.

The recommendations for therapy and prophylaxis of PML are summarized in Table 7.

Cryptosporidiosis

Cryptosporidiosis is a parasitic intestinal disease with fecal–oral transmission, mainly caused *Cryptosporidium parvum* (two other frequent types: *C. hominis* and *C.*

Table 7 Therapy and prophylaxis of progressive multifocal leukoencephalopathy

Therapy/prophylaxis	Drug	Therapeutic regimen
Acute therapy		
First choice	ART	The most important goal is maximal HIV suppression and immune reconstitution. Use intracerebral penetrating agents
Experimental		Only in clinical trials
Prophylaxis		Not available

ART Antiretroviral therapy, HIV human immunodeficiency virus

meleagridis). While diarrhea almost always resolves within a few days in healthy hosts or in HIV-infected patients with CD4 T-cell counts of >200 cells/ μ l, it is often chronic in HIV patients with a CD4 T-cell count of <100 cells/ μ l [169]. Infection of the biliary tract leading to sclerosing cholangitis is frequent, particularly among patients with severe immunodeficiency, but may be reversible with immune reconstitution [170–172] (level of evidence C). Other rare manifestations are infections of the pancreatic duct and pulmonary infections [173, 174].

Treatment

Successful immune reconstitution under ART can lead to complete resolution of clinical cryptosporidiosis [175, 176].

Symptomatic treatment with loperamide and/or tincture of opium should be given. Octreotide (off label) can also be applied. Sufficient hydration is important and infusions may even be required. No specific treatment has been validated [177]. Rifaximin is promising, as first studies with AIDS patients show [178]; however, results from randomized studies are still missing.

Nitazoxanide was found to be effective in a small randomized study in immunocompetent patients [179]. However, this drug is not approved for AIDS patients and showed no effects in a double-blind randomized study in HIV-infected children with cryptosporidiosis [180].

Paromomycin has been found to have favorable effects on diarrhea [181]. However, a double-blind randomized study showed no benefit compared to placebo [182]. In a Cochrane review for the prevention and treatment of cryptosporidiosis, paromomycin did not reduce diarrheal frequency permanently [177].

Prophylaxis

There is no generally accepted prophylaxis, although a protective effect of rifabutin and clarithromycin has been reported from retrospective studies. Azithromycin showed no effect [183]. The usual hygienic measures (gloves) are

Table 8 Therapy and prophylaxis of cryptosporidiosis (daily dose)

Therapy/prophylaxis	Drug	Therapeutic regimen
Acute therapy		
Symptomatic	Loperamide	2–6 \times 2 mg p.o.
	Opium tincture	Opium tincture 1 % = 4 \times 5–15 drops
Symptomatic	Octreotide	2–3 \times 50 μ g s.c. (increase dose slowly)
Curative attempt	Nitazoxanide	2 \times 500 mg
Curative attempt	Rifaximin	2 \times 400 mg
Prophylaxis		Exposure prophylaxis

usually adequate. Patients do not need to be isolated. However, accommodation with other immunosuppressed patients should be avoided.

The recommendations on therapy and prophylaxis of cryptosporidiosis are summarized in Table 8.

For further information, refer to guidelines by the CDC for cryptosporidiosis in HIV-infected patients (CDC 2009; <http://www.cdc.gov/mmwr>) [3].

Cryptococcal infections

Cryptococcosis occurs much more frequently in Africa, the USA, and Southeast Asia than in Europe. Bird droppings (especially of pigeons) are presumably a key reservoir, but a direct transmission between humans has not been observed. Although transmission occurs via inhalation, pulmonary symptoms or lung infiltration are only seen in 30–40 % of cases of HIV-infected patients. Cryptococcosis infection is often followed by disseminated disease in HIV patients with severe immunodeficiency (<100 CD4 T-cells/ μ l) and often involves the CNS (>75 %, meningitis) [21].

Treatment

Recommended treatment for a cryptococcal meningitis is the combination regimen of amphotericin B deoxycholate (AmB-D; 0.7–1.0 mg/kg/day i.v.) and flucytosine (100 mg/kg/day i.v. or p.o. if available), divided into four doses a day. Acute therapy should be given for at least 14 days. If clinical response is good, a switch to monotherapy with fluconazole (400 mg/day) for another 8 weeks is possible [21]. Liposomal amphotericin is slightly more effective than conventional AmB-D and provides an alternative, if AmB-D is not well tolerated [184]. Monotherapy with fluconazole as initial treatment in HIV-infected patients is not sufficient, even with higher daily doses of 800–2,000 mg. Thus, it is only considered as an option in countries with limited resources [21, 185].

In the pre-HAART era, a triple combination therapy with AmB-D, flucytosine, and fluconazole was favored for

the treatment of cryptococcal meningitis in Germany [186]. However, in one randomized study, the triple combination was not more effective than a combination with AmB-D and flucytosine or AmB-D and fluconazole or a monotherapy with AmB-D [187].

The combination with AmB-D and fluconazole is an alternative in regions with limited resources where flucytosine is not available. In a small study in Thailand, a higher dose of fluconazole (800 mg/day) combined with AmB-D (0.7 mg/kg/day) was more effective than monotherapy with AmB-D alone or a regimen of AmB-D + fluconazole (400 mg/day). Other combination therapies (e.g. fluconazole + flucytosine) are possible alternatives, but lack sufficient data [188].

Itraconazole plays no role in primary therapy and is less effective than fluconazole in maintenance therapy [189].

Monotherapy with posaconazole showed a response rate of up to 50 % in a small case study on refractory diseases and therefore provides an alternative for this indication [190]. Efficacy of voriconazole in salvage therapy is still not clear [191]. Echinocandines show no in vitro effect against *C. neoformans*.

In the case of an IRIS when ART is initiated during antimycotic treatment, additional treatment with corticosteroids (0.5–1.0 mg/kg/day prednisolone equivalent) is required [21].

In refractory treatment situations, additional administration of γ -interferon might be useful in individual cases [192].

Treatment success is monitored based on the clinical course and repeated lumbar punctures. Patients should have their intracranial pressure measured at time of diagnosis. If the intracranial pressure is very high, several punctures should be made in the first week until it is reduced to ≤ 20 cm. In individual cases, cerebrospinal fluid (CSF) drainage can be considered to reduce the intracranial pressure if there are no contraindications [21].

For mild, isolated cryptococcal pneumonia (negative CSF diagnosis), monotherapy with fluconazole (400 mg/day) is possible. Treatment should continue for 6–12 months. Severe cases of pneumonia with or without acute respiratory distress syndrome (ARDS) should be treated the same way as meningitis (see above).

ART-naïve patients at the time of diagnosis should start an ART after a 2-week induction therapy with antimycotics. However, an optimal time for initiation of ART is not yet clearly defined.

Prophylaxis

Primary prophylaxis can not be recommended to HIV-infected patients in Germany due to lack of a clear survival benefit [193].

Table 9 Therapy and prophylaxis of cryptococcosis^a

Therapy/ prophylaxis	Drug	Therapeutic regimen
Acute therapy		
Induction therapy (treat at least 2 weeks before switch/de-escalation)		
First choice	Amphotericin B + flucytosine	1 × 0.7 mg/kg/day i.v. or liposomal Amphotericin B (AmBisome®) 1 × 3–4 mg/kg/day i.v. + Ancotil® 4 × 25 mg/kg/day i.v./p.o. or 100 mg/day distributed in four separate doses
De-escalation with good response (at least after 2 weeks)		
First choice	Fluconazole	1 × 400 mg p.o. (For at least 8 more weeks)
Alternatives	Itraconazole	2 × 200 mg p.o. (For at least 8 more weeks)
Primary prophylaxis	Not recommended in Germany	
Secondary prophylaxis	Fluconazole	200 mg/day p.o.
Discontinuation is possible when CD4 T-cell count is >100 cells/μl and HIV-RNA below detection limit for a period of 6 months		

^a Daily doses, unless specified otherwise

After acute therapy of cryptococcal meningitis, secondary prophylaxis should be introduced. Fluconazole (200 mg/day) is the regimen of choice and is also more effective than itraconazole [21]. Secondary prophylaxis can be discontinued after at least 6 months maintenance therapy with sufficient immune reconstitution (>100 CD4 T-cells/μl and HIV-RNA below detection limit for over 6 months). The risk of a relapse is high if maintenance therapy is discontinued too early [194].

The recommendations on therapy and prophylaxis of cryptococcosis are summarized in Table 9.

Infections of nontuberculous mycobacteria

Human immunodeficiency virus-associated infections of nontuberculous mycobacteria (NTM) have declined in countries where ART is available [195–197]. In addition to disseminated NTM diseases, which develop almost exclusively in the setting of severe CD4 T-cell depletion (<50 CD4 T-cells/μl) and which are mainly (>90 %) caused by the *Mycobacterium avium* complex or *M. intracellulare* (*Mycobacterium avium intracellulare* complex, MAI), incidences of NTM-IRIS as well as pulmonary NTM diseases are also observed. Pulmonary NTM is frequently caused by other species, such as *M. kansasii*, *M. xenopi*, *M. malmoense*, and *M. abscessus*. For further information on diagnosis, the reader is referred to the American Thoracic Society criteria [198].

Due to the ubiquitous occurrence of NTM, pre-exposure prophylaxis is not possible and an isolation of infected patients is not necessary. Some specialists, however, recommend a screening of generalized MAI infections in patients with CD4 T-cell counts of $<50/\mu\text{l}$ prior to initiation of an ART.

Treatment

Given here are only recommendations for the MAI therapy. With respect to NTM species other than MAI, the reader is referred to the appropriate literature [198] or advised to consult experts (NTM-NET). A combination treatment of macrolide (clarithromycin or azithromycin) and ethambutol plus/minus rifabutin is recommended [198]. Rifabutin is preferred to rifampicin due to its *in vitro* efficacy against MAI and its lower interaction potential. Following the publication of data showing that rifabutin could be omitted from the treatment regimen [199], another randomized study demonstrated a survival benefit with the triple combination clarithromycin, rifabutin, and ethambutol compared to clarithromycin with either ethambutol or rifabutin—the mortality rate was halved in the treatment arm receiving this triple (clarithromycin-containing) combination [200].

The doses for rifabutin must occasionally be adjusted to the ART regimen [201]. Clarithromycin increases the rifabutin serum level, while rifabutin decreases the clarithromycin level. Treatment duration with rifabutin has not yet been determined in studies; however, experts recommend discontinuing rifabutin after a few weeks and with clinical improvement.

The daily doses for clarithromycin should not exceed 2×500 mg, as a higher mortality risk has been described for patients receiving higher dosages [202, 203]. Azithromycin can be administered instead of clarithromycin, as these two drug are comparably effective in combination with ethambutol, with slightly more rapid sterilization of blood cultures with clarithromycin [196, 199, 204]. As macrolides are the cornerstone of therapy, the development of resistance to macrolides must be avoided, and monotherapy with macrolides should not be administered. In the case of intolerance, alternative substances, such as fluoroquinolone, amikacin, cycloserine, dapson, linezolid, or mefloquine, are available. However, clinical evidence for the treatment of MAI infections with these alternative substances is still insufficient.

In the case of NTM-IRIS, the extent and duration of an antimycobacterial therapy are not clear. It is possible that partial virus suppression is enough for a NTM-specific immune reconstitution [205].

It is easier to evaluate the clinical response to localized NTM infections. In cases of localized lymphadenitis and skin manifestations, therapy duration of 6 months is recommended after patients are culture-negative. If the

clinical response is good and CD4 T-cells continue to increase under a still effective ART, the regimen can be reduced after 3 months to a recurrence prophylaxis with a macrolide for a further 3 months. Patients with abdominal localization have a poorer response and require a more aggressive and longer therapy [206, 207]. Additive corticoid therapy has symptomatic indications.

The treatment of patients with pulmonal NTM diseases not deriving from an IRIS are based on the guidelines for non-HIV-infected patients [198].

Prophylaxis

In the USA, placebo controlled trials for clarithromycin, azithromycin and rifabutin showed that primary prophylaxis significantly reduced MAI-morbidity and -mortality in severely immunocompromised patients [208–211]. All these studies, however, were undertaken in the pre-HA-ART era. In addition, MAI-infections are less frequent in Europe, so that only a few patients receive primary prophylaxis [212]. Due to the declining incidences since the introduction of ART, primary prophylaxis can only avoid a small number of diseases [197]. NTM-associated IRIS can also not be prevented by prophylactic drugs [206].

Therefore primary prophylaxis is not recommended in Germany. After treatment of a disseminated MAI-infection, patients lacking other ART options, should receive secondary prophylaxis with a macrolide, provided CD4 T-cell count is under 50 cells/ μl . Weekly doses of azithromycin are convenient and efficacy is comparable to daily rifabutin [208].

Secondary prophylaxis or maintenance therapy can be discontinued under an ART and if patients are without symptoms and CD4 T-cell count is $>100/\mu\text{l}$ for 6 months.

The recommendations concerning therapy and prophylaxis of disseminated MAI-diseases are summarized in Table 10.

Tuberculosis

Globally, TB is the most prevalent HIV-associated opportunistic infection. In Germany, TB is rare. HIV-infected patients are affected by TB independent of their CD4 T-cell count [213], although incidences increase with advanced immunodeficiency [214].

Treatment

Uncomplicated cases of TB can successfully be treated with a standard therapy regimen over a period of 6 months, regardless of HIV status.

First-line drugs are rifampicin, INH, ethambutol, pyrazinamide, and streptomycin, with INH and rifampicin

Table 10 Therapy and prophylaxis of disseminated *Mycobacterium avium intracellulare* diseases^a

Therapy/ prophylaxis	Drug	Therapeutic regimen
Acute therapy (over 1–2 months)		
First choice	Clarithromycin + Ethambutol + (± Rifabutin)	2 × 500 mg p.o. + 1 × 15 mg/kg body weight p.o. + 1 × 300 mg p.o. ^b
	Alternative Azithromycin + Ethambutol + (± Rifabutin)	1 × 500 mg p.o. + 1 × 15 mg/kg body weight p.o. + 1 × 300 mg p.o. ^b
Maintenance therapy (until CD4 T-cell count >100 cells/μl for >6 months)		
As for acute therapy, but without rifabutin		
Primary prophylaxis		
Not recommended		
Secondary prophylaxis after treated MAI-infection (start if CD4 T-cell count persists at <50/μl; discontinue if CD4 T-cells >100/μl at >6 months)		
First choice	Azithromycin	1 × 1,200 mg/week p.o.
	Alternative Clarithromycin	2 × 500 mg p.o.

Note for Austria: In Austria a 600 mg azithromycin tablet is not available; other doses should be considered

^a Daily doses unless specified otherwise

^b Control of serum level may be necessary with concomitant treatment with ritonavir boosted protease inhibitors; dose adjustment to 150 mg/day is often possible with intensified control of toxicity, reduction to 150 mg per week if necessary. Regular control of nervus opticus under ethambutol

being the most effective. TB should always be treated with a combination of four drugs in the initial phase to prevent drug resistance. Standard initial phase therapy is a 2-month course of rifampicin, INH, ethambutol, and pyrazinamide, followed by a continuation phase therapy of 4 months rifampicin and INH.

In individual cases, such as non-compliance, it may be necessary to extend the standard treatment duration to ≥9 months, especially if sputum cultures are still positive after 2 months. Recurrences after successful therapy appear more frequently in HIV-infected patients [215]. If standard therapy has not been initially applied, treatment should always last for at least 9 months.

Alternatively, ethambutol, streptomycin, and reserve drugs such as ofloxacin or moxifloxacin, cycloserine, and linezolid may be administered. Since this treatment is no different from that for multidrug-resistant TB, these patients should be treated in specialized centers.

Adverse events

Adverse effects occur frequently with anti-TB therapy (refer to individual drug information for side effects,

Table 11 Recommendations for co-administering antiretroviral therapy with rifabutin^a

Drug	Antiretroviral dosage adjustment	Rifabutin dosage adjustment
Boosted protease inhibitors (LPV/r, FPV/r, DRV/r, SQV/r, ATV/r)	None	150 mg every 2 days (or 3×/week)
Efavirenz	None	450 mg/day
Nevirapine	None, but cave hepatotoxicity	
Delavirdine, etravirine	Should not be co-administered	
Maraviroc	Depending on other antiretroviral drugs	Standard dosage
Raltegravir	No data	No data
Nucleoside reverse-transcriptase inhibitors (NRTIs)	None	Standard dosage

^a Modified from CDC 2007 [228]

Unboosted protease inhibitors are no longer recommended due to insufficient plasma levels. Consider TDM

necessary testing, and drug interactions). Severe side effects are observed more often in HIV-infected patients than in HIV-negative patients [216].

ART and TB therapy

Antiretroviral therapy significantly reduces the morbidity and mortality rate in HIV-infected patients [217]. A 6-month TB standard therapy achieves similar success in both HIV-infected and HIV-negative patients [218].

Although a large retrospective and a large open-label, randomized trial showed a survival benefit with simultaneous ART and anti-TB treatment, this approach proves to be difficult in practice due to overlapping drug interactions and side effects [219]. For TB meningitis, side effects are more frequent during the first 2 months of therapy if ART and anti-TB therapy are initiated simultaneously. In this case, a delay of ART by 2 months is possible without risking a higher mortality [220].

With regard to other forms of TB, 25–60 % of patients develop an IRIS in the first 3 months of ART treatment [221]. A consensus on a uniform case definition of TB-IRIS was reached in 2008 [9], which we refer to in the chapter on IRIS of this guideline.

Adherence to simultaneous HIV and *Mycobacterium* TB treatment is difficult to achieve due to the high pill burden and overlapping toxicities. Both rifampicin and protease inhibitors (PIs) are metabolized by cytochrome P450 3A. Concomitant therapy is therefore not recommended [222, 223] (Table 11). Rifabutin can be combined with boosted

Table 12 Dosage adjustment for combination of antiretroviral therapy/rifampicin^a

Drug	Antiretroviral dosage adjustment	Rifampicin dosage adjustment
Efavirenz	600 mg (800 mg for patients >60 kg)	None
Nevirapine	Should not be co-administered	
Etravirine	Should not be co-administered	
Maraviroc	600 mg every 12 h	None
Raltegravir	800 mg every 12 h	None, TDM if possible as RAL levels decrease by 61 %.
NRTIs	None; NRTI combination only is not recommended	

^a Data are from CDC 2007 [228] and OARAC 2009 [230]

PIs, however the dose must be adjusted (Table 12). It may be useful to determine serum levels [201]; however, this approach has not been tested in clinical research with clear endpoints.

Recommendations can be given for first-line ART therapy with tenofovir (TDF), TDF + emtricitabine (FTC), and FTC plus efavirenz in combination with rifampicin-based TB therapy. Alternatives are other efavirenz-based regimens (without adjustment of dose) with rifabutin [222].

To date, clinical data on combinations of rifamycin with new drugs, such as darunavir, raltegravir, or maraviroc, are limited. Due to the strong inducing potential of cytochrome P450 3A, PIs should be avoided and maraviroc should only be given under close observation. Rifampicin also induces the enzyme UGT1A1, leading to increased glucuronidation and reduced plasma levels of raltegravir [224]. No interactions have been reported with tenofovir and T-20 [225].

The recommendations on the adjustment for combination of ART/rifampicin in TB therapy are summarized in Table 12.

Treatment of active TB has clinical priority over ART. In patients with <100 CD4 T-cells/ μ l, simultaneous treatment of both infections is indicated [222, 226]. However, even in this situation it is recommended to start TB therapy first for 2 weeks before initiating ART to prevent possible side effects.

For patients with 100–350 CD4 T-cells/ μ l, ART can be delayed for 2 months until the anti-TB drugs can be reduced for the continuation phase. There is no evidence for an optimal timing of ART when the CD4 T-cell count is >350 cells/ μ l [222]. The results of a large randomized trial indicate that mortality rate in patients with 200–500 CD4 T-cells/ μ l is reduced when ART is initiated during TB therapy [219].

For HIV patients with <50 CD4 T-cells/ μ l, the results of a recent study show a benefit of a delayed ART. The

decision should be made carefully under consideration of the situation of each single patient [17, 227].

HIV-infected patients already on a successful ART should remain on ART, although the regimen may need to be modified [226].

The recommendations for co-administering ART with rifabutin are summarized in the statement that adherence is the most important factor for therapeutic success and to avoid resistant TB strains. The World Health Organization (WHO) recommends a directly observed therapy for these patients.

Treatment of latent TB infection with M. tuberculosis

Latent tuberculosis infection (LTBI) is defined by a positive *Mycobacterium* TB-specific immune response in the tuberculin skin test (TST) or an interferon gamma release assay (IGRA) in the absence of active TB. Clear values for a positive *Mycobacterium* TB-specific immune response in HIV-infected patients do not exist. Patients are not infectious as the TB is not active.

However, HIV-infected patients with LTBI carry a higher risk of developing active TB. According to guidelines for the treatment of LTBI by the CDC [228], HIV-infected patients with a TST of >5 mm should be given treatment with INH for 9 months. This probably also applies to patients with positive IGRA test results, but convincing data are still missing [229]. Alternatively, a 4-month course of rifampicin can be given.

A 2-month course of rifampicin and pyrazinamide is no longer recommended, as it has been associated with significantly higher toxicities in HIV-negative patients [230, 231].

Multidrug resistant and extensively drug-resistant TB

In 2006, 2.2 % of all TB patients showed multidrug resistance (at least resistance against INH and rifampicin). Among these, 5 % were HIV-infected [232]. In addition to incidences of multidrug resistance (MDR), incidences of extensive drug resistance (XDR) were reported in at least 58 countries in 2010 [233]. XDR TB is defined by the WHO as TB which is additionally resistant to fluoroquinolones and at least one of the injectable drugs amikacin, capreomycin, or kanamycin.

Due to the complex therapy and an overall poor prognosis, patients with MDR/XDR TB should be treated in specialized centers.

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Appendix

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