

HIV: primary and secondary prophylaxis for opportunistic infections

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Judith Aberg and William Powderly







ABSTRACT

INTRODUCTION: Opportunistic infections can occur in up to 40% of people with HIV infection and a CD4 count less than 250/mm³, although the risks are much lower with use of highly active antiretroviral treatment. **METHODS AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of prophylaxis for *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis? What are the effects of antituberculosis prophylaxis in people with HIV infection? What are the effects of prophylaxis for disseminated *Mycobacterium avium* complex (MAC) disease for people with, and without, previous MAC disease? What are the effects of prophylaxis for cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella zoster virus (VZV)? What are the effects of prophylaxis for invasive fungal disease in people with, and without, previous fungal disease? What are the effects of discontinuing prophylaxis against opportunistic pathogens in people on highly active antiretroviral treatment (HAART)? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2008 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found 43 systematic reviews, RCTs, or observational studies that met our inclusion criteria. **CONCLUSIONS:** In this systematic review we present information relating to the effectiveness and safety of the following interventions: aciclovir; antituberculosis prophylaxis; atovaquone; azithromycin (alone or plus rifabutin); clarithromycin (alone, or plus rifabutin and ethambutol); discontinuing prophylaxis for CMV, MAC, and PCP; ethambutol added to clarithromycin; famciclovir; fluconazole; isoniazid; itraconazole; oral ganciclovir; rifabutin (alone or plus macrolides); trimethoprim-sulfamethoxazole; and valaciclovir.

QUESTIONS

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INTERVENTIONS

PRIMARY PROPHYLAXIS: PCP AND TOXOPLASMOSIS	 Trade off between benefits and harms
 Likely to be beneficial	Isoniazid for 6 to 12 months (compared with combination treatment for 2–3 months — similar efficacy and less adverse effects, but longer treatment regimen) for primary prophylaxis for tuberculosis
Trimethoprim-sulfamethoxazole (better than placebo, pentamidine aerosol, or dapsone for primary PCP prophylaxis)	11
Trimethoprim-sulfamethoxazole for primary toxoplasmosis prophylaxis (insufficient data from placebo-controlled trials but TMP-SMX and dapsone seem equally effective)	6
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PRIMARY PROPHYLAXIS: TUBERCULOSIS	 Likely to be beneficial
 Beneficial	Azithromycin for primary prophylaxis for MAC
Antituberculosis prophylaxis (better than placebo for primary prophylaxis for tuberculosis)	9
	Clarithromycin for primary prophylaxis for MAC
	13
	 Trade off between benefits and harms
	Macrolides plus rifabutin for primary prophylaxis for MAC
	13
	SECONDARY PROPHYLAXIS: MAC
	 Likely to be beneficial
	Clarithromycin plus ethambutol for secondary MAC prophylaxis (2-drug regimen reduces MAC but unclear

whether adding rifabutin to this confers additional benefit)*	15	DISCONTINUING PRIMARY PROPHYLAXIS IN PEOPLE ON HAART	
SECONDARY PROPHYLAXIS: CMV, HSV, AND VZV		Likely to be beneficial	
Aciclovir for secondary prophylaxis for HSV or VZV*	1 6	Discontinuing primary prophylaxis for PCP and toxoplasmosis in people with CD4 count greater than 200/mm ³	21
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Trade off between benefits and harms		DISCONTINUING SECONDARY PROPHYLAXIS IN PEOPLE ON HAART	
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Likely to be beneficial		Covered elsewhere in Clinical Evidence	
Itraconazole for secondary prophylaxis for <i>Penicillium marneffe</i> (more effective than placebo at preventing relapse)	20	Antiretroviral regimens (see review on HIV infection)	
Likely to be ineffective or harmful		Treating <i>P jirovecii</i> pneumonia in people with HIV	
Itraconazole for secondary prophylaxis for cryptococcal meningitis (less effective than fluconazole for preventing relapse)	20	Footnote	
		*Based on consensus; limited RCT evidence	

Key points

- Opportunistic infections can occur in up to 40% of people with HIV infection and a CD4 count less than 250/mm³, although the risks are much lower with use of highly active antiretroviral treatment (HAART).
HAART has reduced the rate of *Pneumocystis jirovecii* pneumonia (PCP), toxoplasmosis, and other opportunistic infections, so the absolute benefits of prophylactic regimens for opportunistic infections are probably smaller in people with HIV who are also taking HAART, and even smaller for those whose HIV is suppressed.
- Primary prophylaxis with trimethoprim–sulfamethoxazole may reduce the risk of PCP, and has been found to be more effective than pentamidine or dapsone.
Atovaquone may prevent PCP in people who cannot tolerate trimethoprim–sulfamethoxazole.
We don't know whether these drugs prevent toxoplasmosis as we found few RCTs, but there is consensus that standard trimethoprim–sulfamethoxazole prophylaxis or dapsone should offer adequate coverage for toxoplasmosis.
- Tuberculosis can be prevented by standard primary prophylaxis in people who are tuberculin skin test positive.
Short-term combination treatment has similar efficacy to long-term isoniazid monotherapy, but is associated with a greater risk of adverse effects.
- Azithromycin or clarithromycin reduce the risk of disseminated *Mycobacterium avium* complex (MAC) disease as primary prophylaxis for people without prior MAC disease. Adding rifabutin may also be beneficial in this population, but is also associated with an increased risk of adverse effects.

There is consensus that secondary prophylaxis with **clarithromycin plus ethambutol** decreases the risk of relapse in people with previous MAC disease. It remains unclear whether adding rifabutin to the dual drug regimen confers additional benefit as secondary prophylaxis, and the three-drug combination increases adverse effects.

- **Aciclovir** as secondary prophylaxis reduces the risk of herpes simplex virus (HSV) and varicella zoster virus infection (VZV) and all-cause mortality.

Valaciclovir may reduce the risk of recurrent HSV infection, but it may be associated with serious adverse effects.

There is consensus that **famciclovir** is effective as secondary prophylaxis against HSV or VZV and that **ganciclovir** is effective as secondary prophylaxis against CMV, HSV, or VZV.

- **Fluconazole and itraconazole** as primary prophylaxis may reduce the risk of invasive fungal infections, but azoles have been associated with potentially serious interactions with other drugs.

As secondary prophylaxis, **itraconazole** seems effective in reducing relapse of *Penicillium marneffe*, but seems less effective than **fluconazole** at reducing recurrence of cryptococcal meningitis.

- In people who have responded to HAART and have a CD4 cell count greater than 100/mm³ to 200/mm³ (depending on the condition), discontinuation of primary or secondary prophylactic treatment for PCP, toxoplasmosis, MAC, herpes virus, or invasive fungal disease infection seems safe.

DEFINITION Opportunistic infections are intercurrent infections that occur in people infected with HIV. Prophylaxis aims to avoid either the first occurrence of these infections (primary prophylaxis) or their recurrence (secondary prophylaxis, maintenance treatment). This review includes *Pneumocystis jirovecii* pneumonia (PCP), *Toxoplasma gondii* encephalitis, *Mycobacterium tuberculosis*, *Mycobacterium avium* complex (MAC) disease, cytomegalovirus (CMV) disease (most often retinitis), infections from other herpes viruses (herpes simplex virus [HSV] and varicella zoster virus [VZV]), and invasive fungal disease (*Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Penicillium marneffe*).

INCIDENCE/ PREVALENCE The incidence of opportunistic infections is high in people with immune impairment. Data available before the introduction of highly active antiretroviral treatment (HAART) suggest that, with a CD4 count less than 250/mm³, the 2-year probability of developing an opportunistic infection is 40% for PCP, 22% for CMV, 18% for MAC, 6% for toxoplasmosis, and 5% for cryptococcal meningitis.^[1] The introduction of HAART has reduced the rate of opportunistic infections. One cohort study found that the introduction of HAART decreased the incidence of PCP by 94%, CMV by 82%, and MAC by 64%, as presenting AIDS events. HAART decreased the incidence of events subsequent to the diagnosis of AIDS by 84% for PCP, 82% for CMV, and 97% for MAC.^[2]

AETIOLOGY/ RISK FACTORS Opportunistic infections are caused by a wide array of pathogens and result from immune system defects induced by HIV. The risk of developing opportunistic infections increases dramatically with progressive impairment of the immune system. Each opportunistic infection has a different threshold of immune impairment, beyond which the risk increases substantially.^[1] Opportunistic pathogens may infect the immunocompromised host *de novo*, but usually they are simply reactivations of latent pathogens in such hosts.

PROGNOSIS Prognosis depends on the type of opportunistic infection. Even with treatment they may cause serious morbidity and mortality. Most deaths due to HIV infection are caused by opportunistic infections. The absolute benefits of prophylactic regimens for opportunistic infections are probably smaller in people with HIV who are also taking HAART and even smaller for those whose HIV is suppressed. HAART has reduced the rate of PCP, toxoplasmosis, and other opportunistic infections.

AIMS OF INTERVENTION To prevent the occurrence and relapse of opportunistic infections; to discontinue unnecessary prophylaxis; to minimise adverse effects of prophylaxis and loss of quality of life.

OUTCOMES First occurrence of and relapse of opportunistic infections, mortality, and adverse effects of treatments. We have not considered neoplastic diseases associated with specific opportunistic infections. We have considered all-cause mortality as a secondary outcome in this review as many meta-analyses and RCTs were underpowered to detect a clinically important difference between groups in this outcome.

METHODS *Clinical Evidence* search and appraisal March 2008. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2008, Embase 1980 to March 2008, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2008, Issue 1 (1966 to date of issue). An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of

studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We have not excluded "open", "open label", or not blinded trials owing to the ethical and practical difficulties of blinding trials in people with HIV. When assessing effects of primary prophylaxis for specific opportunistic infections, we have included only systematic reviews and RCTs that assessed incidence of infection; we excluded those studies that reported only on mortality without specifying that it was preceded by an opportunistic infection. When assessing invasive fungal disease, we have included only *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Penicillium marneffeii*. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. We also reviewed abstract books/CDs for the following conferences held between 1995 and early 2001: European Clinical AIDS, HIV Drug Treatment, Interscience Conferences on Antimicrobial Agents and Chemotherapy, National Conferences on Human Retroviruses and Opportunistic Infections, and World AIDS Conference. We placed emphasis on systematic reviews and RCTs published after 1993. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see GRADE table, p 30). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of primary prophylaxis for *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis in people with HIV infection?

OPTION TRIMETHOPRIM–SULFAMETHOXAZOLE FOR PRIMARY PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP) PREVENTION

Pneumocystis jirovecii pneumonia (PCP)

Trimethoprim–sulfamethoxazole or pentamidine aerosol compared with placebo Primary prophylaxis with trimethoprim–sulfamethoxazole or pentamidine aerosol (results combined in analysis) may be more effective at reducing the incidence of PCP in people with advanced disease, but we don't know whether trimethoprim–sulfamethoxazole is more effective in people in sub-Saharan Africa with symptomatic (second or third clinical stage in WHO staging system) disease (low-quality evidence).

Trimethoprim–sulfamethoxazole compared with pentamidine aerosol Primary prophylaxis with trimethoprim–sulfamethoxazole may be more effective than aerosolised pentamidine at reducing the incidence of PCP; however, the analysis included data from both primary and secondary prophylaxis (low-quality evidence).

Trimethoprim–sulfamethoxazole compared with dapsons (with or without pyrimethamine) Primary prophylaxis with trimethoprim–sulfamethoxazole may be more effective at preventing PCP; however, the significance of the result varied between different analysis (very low-quality evidence).

High-dose compared with low-dose trimethoprim–sulfamethoxazole We don't know how primary prophylaxis with higher-dose trimethoprim–sulfamethoxazole compares with lower-dose trimethoprim–sulfamethoxazole at reducing rates of PCP infection (very low-quality evidence).

Mortality

Trimethoprim–sulfamethoxazole or pentamidine aerosol compared with placebo We don't know whether primary prophylaxis with trimethoprim–sulfamethoxazole or pentamidine aerosol is more effective at reducing all-cause mortality (low-quality evidence).

Trimethoprim–sulfamethoxazole compared with pentamidine aerosol We don't know how effective trimethoprim–sulfamethoxazole is at reducing all-cause mortality compared with aerosolised pentamidine (low-quality evidence).

Trimethoprim–sulfamethoxazole compared with dapsone (with or without pyrimethamine) We don't know how effective trimethoprim–sulfamethoxazole is at reducing all-cause mortality compared with dapsone (very low-quality evidence).

High-dose compared with low-dose trimethoprim–sulfamethoxazole We don't know how primary prophylaxis with higher-dose trimethoprim–sulfamethoxazole compares with lower-dose trimethoprim–sulfamethoxazole at reducing all-cause mortality (very low-quality evidence).

Note

In general, trials of PCP prophylaxis were conducted before the advent and widespread use of highly active antiretroviral treatment (HAART) and thus their results should be interpreted with caution. Although this is unlikely to affect the comparative results, HAART has resulted in a large decrease in the rate of PCP and other opportunistic infections; therefore, the absolute benefits of these prophylactic regimens are probably smaller when used with HAART.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: **Trimethoprim–sulfamethoxazole or pentamidine aerosol versus placebo for primary PCP prophylaxis:**

We found one systematic review^[3] analysing the effects of trimethoprim–sulfamethoxazole (TMP-SMX; co-trimoxazole) or pentamidine aerosol versus placebo, and one subsequent RCT.^[4]

The systematic review (search date not reported) found that prophylaxis with TMP-SMX or pentamidine aerosol significantly reduced the incidence of *Pneumocystis jirovecii* pneumonia (PCP) compared with placebo (6 RCTs [1 of TMP-SMX, 5 of pentamidine aerosol, some open label, no further data on blinding reported], 823 people with advanced disease in total; *P jirovecii* events: RR 0.39, 95% CI 0.27 to 0.55; absolute numbers not reported so unclear how many people in the analysis of this outcome).^[3] The review found no significant difference in all-cause mortality between TMP-SMX or pentamidine aerosol and placebo (RR 0.87, 95% CI 0.60 to 1.25; absolute numbers not reported so unclear how many people in the analysis of this outcome). The single open-label RCT from the review that compared TMP-SMX versus placebo (60 HIV-positive people with a new diagnosis of Kaposi's sarcoma) found that proportionately fewer people taking TMP-SMX than placebo developed PCP over 24 months (0/30 [0%] with TMP-SMX v 16/30 [53%] with placebo; significance not reported).^[5] The RCT found that TMP-SMX significantly reduced all-cause mortality over 3 years compared with placebo (18/30 [60%] with TMP-SMX v 28/30 [93%] with placebo; *P* less than 0.002).

The subsequent double-blind RCT (545 people in sub-Saharan Africa with symptomatic disease; second or third clinical stage disease in the WHO staging system; regardless of CD4 cell count) compared TMP-SMX versus placebo and found no significant difference between groups in incidence of PCP (no cases of PCP reported) or all-cause mortality over 12 months (41/245 [17%] with TMP-SMX v 46/238 [19%] with placebo; HR 0.87, 95% CI 0.57 to 1.32; *P* = 0.51).^[4]

Trimethoprim–sulfamethoxazole versus pentamidine aerosol for primary PCP prophylaxis:

We found one systematic review (search date not reported), which found that TMP-SMX significantly reduced the incidence of PCP compared with aerosolised pentamidine (14 RCTs of both primary and secondary prophylaxis for PCP, some open label, no further data on blinding reported, 2248 people in total; *P jirovecii* events: RR 0.58, 95% CI 0.45 to 0.75; absolute numbers not reported so unclear how many people included in the analysis of this outcome).^[3] The review found no significant difference in all-cause mortality between TMP-SMX and aerosolised pentamidine (2248 people; RR 0.99, 95% CI 0.80 to 1.22; absolute numbers not reported so unclear how many people included in the analysis of this outcome).

Trimethoprim–sulfamethoxazole versus dapsone (with or without pyrimethamine) for primary PCP prophylaxis:

We found two systematic reviews.^[3] ^[6]

The first systematic review (search date not reported) found no significant difference in rates of PCP between TMP-SMX and dapsone (with or without pyrimethamine), although the incidence of PCP was lower in people taking TMP-SMX (8 RCTs of both primary and secondary prophylaxis for PCP, some open label, no further data on blinding reported, 1957 people in total; RR 0.61, 95% CI 0.34 to 1.10; absolute numbers not reported so unclear how many people in the analysis of this outcome).^[3] The review found no significant difference in all-cause mortality between TMP-SMX and dapsone (RR 0.95, 95% CI 0.82 to 1.11; absolute numbers not reported so unclear how many people in the analysis of this outcome).

The second systematic review (search date not reported) found that TMP-SMX was significantly more effective in preventing PCP than dapsone/pyrimethamine (8 RCTs, 3 identified by the first

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review, ^[3] some of which were open label, 2087 people in total; RR 0.49, 95% CI 0.26 to 0.92; absolute numbers not reported so unclear how many people in the analysis of this outcome). ^[6] The review found no significant difference in all-cause mortality between TMP-SMX and dapsone/pyrimethamine (RR 0.98, 95% CI 0.80 to 1.08; absolute numbers not reported so unclear how many people in the analysis of this outcome).

High-dose versus low-dose trimethoprim–sulfamethoxazole for primary PCP prophylaxis: We found one systematic review ^[3] and one subsequent RCT. ^[7]

The systematic review (search date not reported) found similar rates of PCP infection in people taking lower-dose (160/800 mg 3 times/week or 80/400 mg/day) and higher-dose (160/800 mg/day) TMP-SMX (failure rate per 100 person-years 1.8, 95% CI 1.0 to 3.3 with lower dose v 0.5, 95% CI 0 to 2.9 with higher dose; absolute numbers and significance not reported). ^[3] The review did not assess all-cause mortality for this comparison.

The subsequent open-label RCT (2625 people) also found no significant difference in the rate of PCP infection in people who received TMP-SMX 160/800 mg daily compared with three times weekly (3.5/100 person-years with daily dose v 4.1/100 person-years with 3 times-weekly dose; RR 0.82, 95% CI 0.61 to 1.09; P = 0.16). ^[7] There was no significant difference in all-cause mortality between groups (18.9/100 person-years with daily dose v 18.5/100 person-years with 3 times-weekly dose; RR 0.96, 95% CI 0.04 to 1.01; P = 0.12).

Harms:

Trimethoprim–sulfamethoxazole versus placebo for primary PCP prophylaxis:

One RCT in sub-Saharan Africa found that TMP-SMX reduced serious events (death or hospital admission, irrespective of the cause) compared with placebo, regardless of their initial CD4 cell count (HR 0.57, 95% CI 0.43 to 0.75; P less than 0.001). ^[4] It also found that TMP-SMX significantly increased moderate neutropenia compared with placebo (AR: 62/271 [23%] with TMP-SMX v 26/244 [10%] with placebo; RR 2.1, 95% CI 1.4 to 3.3; NNH 8, 95% CI 5 to 14). Two RCTs (largest 377 people) found that gradual initiation of TMP-SMX may improve tolerance of the regimen compared with abrupt initiation. ^[8] ^[9] Two RCTs (238 people, 50 people) found no significant benefit from acetylcysteine in preventing TMP-SMX hypersensitivity reactions in HIV-infected people. ^[10] ^[11]

High-dose versus low-dose trimethoprim–sulfamethoxazole for primary PCP prophylaxis:

The systematic review found that severe adverse effects (predominantly rash, fever, and haematological effects leading to discontinuation within 1 year) occurred in proportionately more people taking higher doses of TMP-SMX than in those taking lower doses (25% with higher doses v 15% with lower doses). ^[3] The subsequent RCT comparing high-dose with low-dose TMP-SMX found significantly higher rates of discontinuation because of adverse effects in people taking high doses of TMP-SMX (RR 2.14; P less than 0.001). ^[7]

Pentamidine aerosol for primary PCP prophylaxis:

Bronchospasm occurred in 3% of people taking aerosolised pentamidine 300 mg monthly. ^[3]

Comment:

Clinical guide:

Role of highly active antiretroviral treatment (HAART):

We found more than 50 RCTs on the prophylaxis of PCP, toxoplasmosis, or both, but their results should be interpreted with caution because they were conducted mostly before the advent and widespread use of HAART. Although this is unlikely to affect the comparative results, HAART has resulted in a large decrease in the rate of PCP, toxoplasmosis, and other opportunistic infections; therefore, the absolute benefits of these prophylactic regimens are probably smaller when used with HAART.

Prophylaxis in Africa:

Beneficial effects of TMP-SMX in Africa may be largely because of prophylaxis for bacterial infections rather than PCP.

OPTION**TRIMETHOPRIM-SULFAMETHOXAZOLE FOR PRIMARY TOXOPLASMOSIS PREVENTION****Toxoplasmosis**

Trimethoprim–sulfamethoxazole compared with placebo We don't know whether primary prophylaxis with trimethoprim–sulfamethoxazole is more effective at reducing the incidence of toxoplasmosis in people in sub-Saharan Africa with symptomatic (second or third clinical stage in WHO staging system) disease (low-quality evidence).

Trimethoprim–sulfamethoxazole compared with dapsone (with or without pyrimethamine) We don't know how effective trimethoprim–sulfamethoxazole is at preventing toxoplasmosis compared with dapsone (with or without pyrimethamine); however, the analysis included data from both primary and secondary prophylaxis (low-quality evidence).

High-dose compared with low-dose trimethoprim–sulfamethoxazole We don't know whether primary prophylaxis with higher-dose trimethoprim–sulfamethoxazole is more effective than lower-dose trimethoprim–sulfamethoxazole at reducing rates of toxoplasmosis infection ([very-low-quality evidence](#)).

Mortality

Trimethoprim–sulfamethoxazole compared with placebo We don't know whether primary prophylaxis with trimethoprim–sulfamethoxazole is more effective at improving overall survival in people in sub-Saharan Africa with symptomatic (second or third clinical stage in WHO staging system) disease (low-quality evidence).

Trimethoprim–sulfamethoxazole compared with dapsone (with or without pyrimethamine) We don't know how effective primary prophylaxis with trimethoprim–sulfamethoxazole is at reducing all-cause mortality compared with dapsone (with or without pyrimethamine); however, the analysis included data from both primary and secondary prophylaxis (low-quality evidence).

High-dose compared with low-dose trimethoprim–sulfamethoxazole We don't know how primary prophylaxis with higher-dose trimethoprim–sulfamethoxazole compares with lower-dose trimethoprim–sulfamethoxazole at reducing all-cause mortality (very low-quality evidence).

Note

In general, trials of toxoplasmosis prophylaxis were conducted before the advent and widespread use of highly active antiretroviral treatment (HAART) and thus their results should be interpreted with caution. Although this is unlikely to affect the comparative results, HAART has resulted in a large decrease in the rate of toxoplasmosis and other opportunistic infections; therefore, the absolute benefits of these prophylactic regimens are probably smaller when used with HAART.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see [GRADE table, p 30](#).

Benefits:

Trimethoprim–sulfamethoxazole versus placebo for primary toxoplasmosis prophylaxis:

We found one systematic review (search date not reported) ^[3] analysing the effects of trimethoprim–sulfamethoxazole (TMP-SMX; co-trimoxazole) or pentamidine aerosol versus placebo, and one subsequent RCT. ^[4] The review did not assess rates of toxoplasmosis for this comparison. ^[3] The subsequent double-blind RCT (545 people in sub-Saharan Africa with symptomatic disease; second or third clinical stage disease in the [WHO staging system](#); regardless of CD4 cell count) compared TMP-SMX versus placebo, and found no significant difference in incidence of toxoplasmosis between groups (1/271 [0.4%] with TMP-SMX *v* 6/270 [2%] with placebo; *P* = 0.20). ^[4] The RCT also found no significant difference between groups in all-cause mortality over 12 months (41/245 [17%] with TMP-SMX *v* 46/238 [19%] with placebo; HR 0.87, 95% CI 0.57 to 1.32; *P* = 0.51). However, the RCT may have been underpowered to detect a clinically important difference in outcomes between groups.

Trimethoprim–sulfamethoxazole versus dapsone (with or without pyrimethamine) for primary toxoplasmosis prophylaxis:

We found one systematic review. ^[6] The review (search date not reported) found no significant difference between TMP-SMX and dapsone/pyrimethamine in preventing toxoplasmosis (8 RCTs, of both primary and secondary prophylaxis, some open label, no further data on blinding reported, 1618 people in total; RR 1.17, 95% CI 0.68 to 2.04; absolute numbers not reported so unclear how many people in the analysis of this outcome). The review found no significant difference in all-cause mortality between TMP-SMX and dapsone (RR 0.95, 95% CI 0.82 to 1.11; absolute numbers not reported so unclear how many people in the analysis of this outcome).

High-dose versus low-dose trimethoprim–sulfamethoxazole for primary toxoplasmosis prophylaxis:

We found one open-label RCT (2625 people). ^[7] The RCT found no significant difference in the rate of toxoplasmosis in people who received TMP-SMX 160/800 mg daily compared with three times weekly (1.8/100 person-years with daily dose *v* 1.8/100 person-years with 3 times-weekly dose; RR 1.02, 95% CI 0.39 to 2.63). There was no significant difference in all-cause mortality between groups (18.9/100 person-years with daily dose *v* 18.5/100 person-years with 3 times-weekly dose; RR 0.96, 95% CI 0.04 to 1.01; *P* = 0.12).

Harms:

See harms of trimethoprim–sulfamethoxazole for PCP, p 4.

Comment:

Clinical guide:

Concomitant coverage for toxoplasmosis and PCP:

Standard TMP-SMX prophylaxis or dapsone should offer adequate coverage for toxoplasmosis. Pentamidine aerosol has no intrinsic activity against *Toxoplasma gondii*. It is advisable to assess

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toxoplasmosis risk if the CD4 count is less than $100/\text{mm}^3$ and there is positive toxoplasma serology.^[1]

Role of highly active antiretroviral treatment (HAART):

We found more than 50 RCTs on the prophylaxis of PCP, toxoplasmosis, or both, but their results should be interpreted with caution because they were conducted mostly before the advent and widespread use of HAART. Although this is unlikely to affect the comparative results, HAART has resulted in a large decrease in the rate of PCP, toxoplasmosis, and other opportunistic infections; therefore, the absolute benefits of these prophylactic regimens are probably smaller when used with HAART.

OPTION**ATOVAQUONE FOR PRIMARY PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP) OR TOXOPLASMOSIS PREVENTION****Pneumocystis jirovecii pneumonia (PCP)**

Atovaquone compared with pentamidine aerosol We don't know how primary prophylaxis with atovaquone compares with aerosolised pentamidine at reducing the incidence of PCP at 11 months in people intolerant of trimethoprim-sulfamethoxazole; however, the analysis included data from both primary and secondary prophylaxis (*very low-quality evidence*).

Atovaquone compared with dapsone We don't know how primary prophylaxis with atovaquone compares with dapsone at reducing the incidence of PCP in people aged over 13 years who are intolerant of trimethoprim-sulfamethoxazole (*low-quality evidence*).

Mortality

Atovaquone compared with dapsone We don't know how primary prophylaxis with atovaquone compares with dapsone at reducing all-cause mortality in people aged over 13 years who are intolerant of trimethoprim-sulfamethoxazole (*low-quality evidence*).

Note

We found no direct information from RCTs about whether primary prophylaxis with atovaquone is better than no active treatment at preventing PCP or toxoplasmosis. In clinical practice, atovaquone is usually used in people who are either intolerant of or fail to respond to trimethoprim-sulfamethoxazole. It would be considered unethical to perform a trial comparing atovaquone versus placebo. In general, trials of toxoplasmosis prophylaxis were conducted before the advent and widespread use of highly active antiretroviral treatment (HAART) and thus their results should be interpreted with caution. Although this is unlikely to affect the comparative results, HAART has resulted in a large decrease in the rate of toxoplasmosis and other opportunistic infections; therefore, the absolute benefits of these prophylactic regimens are probably smaller when used with HAART.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits:**Atovaquone versus placebo for primary PCP prophylaxis:**

We found no RCTs (see comment below).

Atovaquone versus pentamidine aerosol for primary PCP prophylaxis:

We found one open-label RCT (549 people intolerant of trimethoprim-sulfamethoxazole, 42% of whom had a history of *Pneumocystis jirovecii* pneumonia [PCP]), which compared three treatments: high-dose atovaquone (1500 mg/day), low-dose atovaquone (750 mg/day), and aerosolised pentamidine (300 mg monthly).^[12] The RCT did not report results for primary and secondary prophylaxis separately. It was designed to detect a 50% difference in rates of PCP between either atovaquone regimen and pentamidine aerosol and made adjustments for multiple comparisons when assessing between group differences. It found no significant difference between treatments in the incidence of PCP or mortality after a median follow-up of 11.3 months (incidence of PCP: 47/188 [26%] with low-dose atovaquone v 39/175 [22%] with high-dose atovaquone v 31/186 [17%] with pentamidine aerosol; low-dose atovaquone v pentamidine aerosol: RR 1.41, 95% CI 0.90 to 2.22; high-dose atovaquone v pentamidine aerosol: RR 1.26, 95% CI 0.78 to 2.03; mortality: 42/188 [22%] with low-dose atovaquone v 27/175 [15%] with high-dose atovaquone v 36/186 [19%] with pentamidine aerosol; low-dose atovaquone v pentamidine aerosol: RR 1.12, 95% CI 0.72 to 1.75; high-dose atovaquone v pentamidine aerosol: RR 0.75, 95% CI 0.46 to 1.24).^[12]

Atovaquone versus dapsone for primary PCP prophylaxis:

One open-label RCT found no significant difference between atovaquone 1500 mg daily and dapsone 100 mg daily in the incidence of PCP infection (1057 people aged over 13 years, intolerant of trimethoprim-sulfamethoxazole, of whom 298 had a history of PCP; cases of PCP per 100 person-years in people receiving primary prophylaxis: 11.3 with atovaquone v 14.1 with dapsone; RR 0.81, 95% CI 0.58 to 1.12; $P = 0.20$).^[13] The RCT also found no significant difference in all-cause mor-

HIV: primary and secondary prophylaxis for opportunistic infections

tality between groups (mortality per 100 person-years in people receiving primary prophylaxis: 23.2 with atovaquone v 18.6 with dapsone; RR 1.25, 95% CI 0.98 to 1.59; P = 0.07).

Atovaquone for primary toxoplasmosis prophylaxis:

We found no systematic review or RCTs.

Harms:**Atovaquone versus placebo for primary PCP prophylaxis:**

We found no RCTs.

Atovaquone versus pentamidine aerosol for primary PCP prophylaxis:

In one open-label RCT, treatment-limiting adverse events were more common with atovaquone than with pentamidine aerosol (16% with low-dose atovaquone v 25% with high-dose atovaquone v 7% with pentamidine aerosol; P less than 0.01).^[12]

Atovaquone versus dapsone for primary PCP prophylaxis:

One open-label RCT comparing atovaquone versus dapsone found no significant difference between treatments in the overall risk of stopping treatment owing to adverse effects (RR 0.94, 95% CI 0.74 to 1.19).^[13] Atovaquone was stopped significantly more frequently than dapsone in people receiving dapsone at baseline (RR 3.78, 95% CI 2.37 to 6.01), and significantly less frequently in people not receiving dapsone at baseline (RR 0.42, 95% CI 0.30 to 0.58).

Atovaquone for primary toxoplasmosis prophylaxis:

We found no RCTs.

Comment:**Clinical guide:**

In clinical practice, atovaquone is usually used in people who are either intolerant of or fail to respond to trimethoprim–sulfamethoxazole. It would be considered unethical to perform a trial comparing atovaquone versus placebo.

Role of highly active antiretroviral treatment (HAART):

We found more than 50 RCTs on the prophylaxis of PCP, toxoplasmosis, or both, but their results should be interpreted with caution because they were conducted mostly before the advent and widespread use of HAART. Although this is unlikely to affect the comparative results, HAART has resulted in a large decrease in the rate of PCP, toxoplasmosis, and other opportunistic infections; therefore, the absolute benefits of these prophylactic regimens are probably smaller when used with HAART.

QUESTION

What are the effects of primary antituberculosis prophylaxis in people with HIV infection?

OPTION

ANTITUBERCULOSIS PROPHYLACTIC REGIMENS VERSUS PLACEBO

Tuberculosis

Antituberculosis prophylactic regimens compared with placebo Primary prophylaxis with antituberculosis regimens seems more effective at reducing the incidence of active tuberculosis at 1 to 3 years in adults who are HIV and tuberculin skin test positive, but we don't know whether it is more effective in adults with HIV who are tuberculin skin test negative. Primary prophylaxis with isoniazid seems more effective at reducing the incidence of tuberculosis at 6 months in children of average age 2 years who are tuberculin skin test negative (*moderate-quality evidence*).

Mortality

Antituberculosis prophylactic regimens compared with placebo We don't know whether primary prophylaxis with antituberculosis regimens is more effective at reducing mortality (death from any cause) in adults with HIV who are tuberculin skin test positive or negative. Primary prophylaxis with isoniazid may be more effective at reducing mortality at 6 months in children of average age 2 years who are tuberculin skin test negative (*low-quality evidence*).

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits:**Antituberculosis regimens versus placebo:**

We found one systematic review (search date 2002, 13 RCTs, most single blind, 5664 HIV-positive adults from Haiti, Kenya, Spain, Uganda, the USA, and Zambia)^[14] and two subsequent RCTs comparing antituberculosis regimens versus placebo.^{[15] [16]}

The RCTs identified by the review compared isoniazid (6–12 months) or combination treatment (rifampicin plus pyrazinamide, isoniazid plus rifampicin, or isoniazid plus rifampicin plus pyrazinamide, for 2–3 months) versus placebo. Mean follow-up varied from 1 to 3 years. The main outcomes, stratified by tuberculin skin test positivity, were tuberculosis (TB; either microbiological or clinical) and death (from any cause). The review found that antituberculosis prophylaxis significantly

reduced the incidence of active TB in tuberculin skin test-positive adults compared with placebo (4 RCTs, 2378 people; incidence of active TB: 39/1760 [2%] with treatment v 46/618 [7%] with placebo; RR 0.38, 95% CI 0.25 to 0.57).^[14] In tuberculin skin test-positive people, it also found no significant difference between prophylaxis and placebo in the risk of death from any cause (4 RCTs, 2378 people; 195/1760 [11%] with treatment v 84/618 [14%] with placebo; RR 0.80, 95% CI 0.63 to 1.02). In tuberculin skin test-negative adults the review found no significant difference between antituberculosis prophylaxis and placebo in the risk of TB or death from any cause (TB; 7 RCTs, 2822 people: 66/1629 [4.1%] with treatment v 54/1193 [4.5%] with placebo; RR 0.83, 95% CI 0.58 to 1.18; death from any cause: 373/1629 [23%] with treatment v 298/1193 [25%] with placebo; RR 1.02, 95% CI 0.89 to 1.15).^[14]

Two RCTs included in the systematic review reported the results of long-term follow-up of antituberculosis prophylaxis on the risk of TB infection.^{[17] [18]} The first RCT (open-label design) compared isoniazid or rifampicin plus pyrazinamide versus placebo after a mean of 3 years' follow-up (see comment below).^[17] Intention-to-treat analysis found that, overall, isoniazid or rifampicin plus pyrazinamide significantly reduced the overall risk of TB at 2.5 years compared with placebo (1053 Zambian adults; 161 tuberculin skin test positive, 517 negative, the rest unknown; cumulative RR of TB 0.55, 95% CI 0.32 to 0.93), although the benefit diminished over this time.^[14]

The second RCT (single-blind design) compared four treatments: isoniazid, isoniazid plus rifampicin, isoniazid plus rifampicin plus pyrazinamide, and placebo.^[18] It found no significant difference between isoniazid (given for 6 months) and placebo in the risk of active TB in tuberculin-positive people at 3 years (2736 Ugandan adults, 2018 tuberculin skin test positive and 718 negative; RR 0.67, 95% CI 0.42 to 1.07). However, it found that isoniazid plus rifampicin (for 3 months), or isoniazid plus rifampicin plus pyrazinamide (for 3 months) significantly reduced the risk of active TB infection in tuberculin-positive people compared with placebo at 3 years (isoniazid plus rifampicin v placebo adjusted RR 0.49, 95% CI 0.29 to 0.82; isoniazid plus rifampicin plus pyrazinamide v placebo adjusted RR 0.41, 95% CI 0.22 to 0.76). It found no significant difference between isoniazid (given for 6 months) and placebo in people with a negative tuberculin skin test at 1 or 2 years' follow-up (at 1 year: RR 0.74, 95% CI 0.30 to 1.79; at 2 years: adjusted RR 0.61, 95% CI 0.32 to 1.16).^[18] The RCT did not assess all-cause mortality in people taking antituberculosis drugs compared with placebo.

The first subsequent double-blind RCT (118 adults in South Africa with WHO stage 3 or 4 HIV, 98 tuberculin skin test negative) compared isoniazid versus placebo for 12 months.^[15] All participants received pyridoxine 25 mg twice weekly. The RCT found no significant difference in rates of TB infection between isoniazid and placebo at 2 years (analysis of 98 TB skin test-negative people: 18/100 person-years with isoniazid v 11.6/100 person-years with placebo; $P = 0.42$). It also found no significant difference between groups in all-cause mortality but was underpowered to detect clinically important differences in this outcome (14/48 [29%] with isoniazid v 18/50 [36%] with placebo; $P = 0.32$). Compliance with treatment as measured by pill counts and patient-nominated supervisor records was high (median 85% of all participants), with no significant difference in compliance between groups.

The second subsequent double-blind RCT (277 children in South Africa with HIV, median age 24.7 months, 235 tuberculin skin test negative) compared isoniazid versus placebo for a mean 5.7 months.^[16] The RCT was stopped early owing to a significant increase in mortality for any cause, primarily sepsis ($P = 0.0002$), in children receiving placebo. It found that isoniazid significantly reduced the incidence of TB at a mean 5.7 months compared with placebo (proportion with TB: 5/132 [4%] with isoniazid v 13/131 [10%] with placebo; HR 0.28, 95% CI 0.10 to 0.78).

Harms:

Antituberculosis regimens versus placebo:

The systematic review found that antituberculosis prophylaxis significantly increased the risk of adverse events resulting in stopping of treatment compared with placebo (7 RCTs; 5427 people: 137/3554 [4%] with antituberculosis prophylaxis v 33/1873 [2%] with placebo; RR 2.49, 95% CI 1.64 to 3.77).^[14]

The first subsequent RCT gave no information on adverse effects.^[15]

The second subsequent RCT found similar rates of grade 3 or 4 toxicity in both groups (5/132 [4%] with isoniazid v 8/131 [6%] with placebo; significance assessment not reported).^[16]

Comment:

In one of the RCTs included in the review,^[14] many people taking placebo were offered isoniazid after randomisation.^[17]

Clinical guide:

Without prophylaxis, people who are HIV and tuberculin skin test positive have a 50% or more lifetime risk of developing tuberculosis compared with a 10% lifetime risk in people who are HIV positive but tuberculin skin test negative.^[19] Clinical features of TB may be atypical in people with HIV infection and diagnosis may be more difficult, disease progression more rapid, and outcome worse.

OPTION**DIFFERENT ANTITUBERCULOSIS PROPHYLACTIC REGIMENS VERSUS EACH OTHER****Tuberculosis**

Different antituberculosis prophylactic regimens compared with each other We don't know how primary prophylaxis with isoniazid monotherapy for 6 to 12 months compares with combination treatment (isoniazid plus rifampicin, rifampicin plus pyrazinamide, or isoniazid plus rifampicin plus pyrazinamide) for 2 to 3 months at reducing the risk of active tuberculosis in people who are HIV positive (*low-quality evidence*).

Mortality

Different antituberculosis prophylactic regimens compared with each other We don't know how primary prophylaxis with isoniazid monotherapy for 6 to 12 months compares with combination treatment (isoniazid plus rifampicin, rifampicin plus pyrazinamide, or isoniazid plus rifampicin plus pyrazinamide) for 2 to 3 months at reducing mortality (death from any cause) in people who are HIV positive (*low-quality evidence*).

Adverse effects

Different antituberculosis prophylactic regimens compared with each other Primary prophylaxis with combination treatment (isoniazid plus rifampicin, rifampicin plus pyrazinamide, or isoniazid plus rifampicin plus pyrazinamide) for 2 to 3 months may be associated with an increase in the proportion of people who discontinue treatment because of adverse effects compared with isoniazid monotherapy for 6 to 12 months (*low-quality evidence*).

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits:**Different antituberculosis prophylactic regimens versus each other:**

We found one systematic review (search date 2002, 13 RCTs, most single blind, 5664 HIV-positive adults from Haiti, Kenya, Spain, Uganda, the USA, and Zambia).^[14] The review found no significant difference in the risk of active tuberculosis (TB) or death (any cause) between isoniazid monotherapy for 6 to 12 months and combination treatment (isoniazid plus rifampicin, rifampicin plus pyrazinamide, or isoniazid plus rifampicin plus pyrazinamide) for 2 to 3 months (TB: 3 RCTs, 1390 people; 14/683 [2.05%] with isoniazid v 14/707 [1.98%] with isoniazid plus rifampicin; RR 1.05, 95% CI 0.51 to 2.17; death: 4 RCTs, 1385 people; 71/683 [10.4%] with isoniazid v 67/702 [10.0%] with isoniazid plus rifampicin; RR 1.09, 95% CI 0.80 to 1.50; TB: 6 RCTs, 3196 people; 73/1597 [4.57%] with isoniazid v 73/1599 [4.56%] with rifampicin plus pyrazinamide; RR 1.00, 95% CI 0.73 to 1.38; death: 6 RCTs, 3137 people; 299/1597 [18.7%] with isoniazid v 283/1540 [18.4%] with rifampicin plus pyrazinamide; RR 1.03, 95% CI 0.89 to 1.19; TB: 1 RCT, 998 people; 7/536 [1%] with isoniazid v 10/462 [2%] isoniazid plus rifampicin plus pyrazinamide; RR 0.60, 95% CI 0.23 to 1.57; death: 1 RCT, 998 people; 58/536 [11%] with isoniazid v 58/462 [13%] isoniazid plus rifampicin plus pyrazinamide; RR 0.86, 95% CI 0.61 to 1.21).^[14]

Harms:**Different antituberculosis prophylactic regimens versus each other:**

The review found that combination treatment (for 2–3 months) increased the risk of treatment discontinuation due to adverse effects compared with isoniazid monotherapy for 6 to 12 months (3 RCTs, 1390 people; 24/683 [4%] with isoniazid v 33/707 [5%] with isoniazid plus rifampicin; RR 0.75, 95% CI 0.46 to 1.24; 4 RCTs, 3196 people; 66/1597 [4%] with isoniazid v 102/1599 [6%] with rifampicin plus pyrazinamide; RR 0.64, 95% CI 0.48 to 0.86; 1 RCT, 998 people; 3/536 [1%] with isoniazid v 26/462 [6%] with isoniazid plus rifampicin plus pyrazinamide; RR 0.10, 95% CI 0.03 to 0.33).^[14]

Comment:

The review did not find significant heterogeneity in outcomes in people whose tuberculin skin test result at baseline was positive, negative, or unknown.^[14] Less than half of the RCTs included in the systematic review reported on adherence to treatment and the definition of adherence varied between studies. One RCT identified by the review found higher rates of adherence with a 2-month course of rifampicin plus pyrazinamide compared with 6 months of isoniazid. A second RCT identified by the review reported better adherence with 3 months of isoniazid plus rifampicin compared with 12 months of isoniazid. The remaining RCT identified by the review found no difference in adherence among individuals receiving isoniazid for 6 months, isoniazid plus rifampicin for 3 months, and isoniazid plus rifampicin plus pyrazinamide for 3 months.

Clinical guide:

There is concern about emergence of rifampicin resistance if this drug is used in antituberculosis prophylaxis, although we found no reports of this. There is a theoretical risk that widespread, unsupervised use of isoniazid alone could promote resistance to this drug, although we found no evidence that this has happened.

QUESTION What are the effects of primary prophylaxis for disseminated *Mycobacterium avium* complex (MAC) disease in people with HIV infection without previous MAC disease?

OPTION AZITHROMYCIN FOR PRIMARY PROPHYLAXIS FOR M AVIUM COMPLEX (MAC)

Mycobacterium avium complex (MAC)

Azithromycin compared with placebo Primary prophylaxis with azithromycin may be more effective at reducing the incidence of MAC at 30 days in people with AIDS and CD4 count less than 100/mm³ (low-quality evidence).

Azithromycin alone compared with rifabutin alone or compared with azithromycin plus rifabutin Primary prophylaxis with azithromycin alone seems more effective than rifabutin alone at reducing the incidence of MAC at 1 year in HIV-positive people. Primary prophylaxis with azithromycin alone and rifabutin alone seems less effective than azithromycin plus rifabutin at reducing the incidence of MAC at 1 year in HIV-positive people (moderate-quality evidence).

Mortality

Azithromycin compared with placebo We don't know whether primary prophylaxis with azithromycin is more effective at reducing all-cause mortality at 12 months in people with AIDS and CD4 count less than 100/mm³ (very low-quality evidence).

Azithromycin alone compared with rifabutin alone or compared with azithromycin plus rifabutin Primary prophylaxis with azithromycin alone, rifabutin alone, and with azithromycin plus rifabutin, seems equally effective at reducing all-cause mortality in HIV-positive people (moderate-quality evidence).

Adverse effects

Azithromycin alone compared with rifabutin alone or compared with azithromycin plus rifabutin Dose-limiting toxicity may be less likely with azithromycin alone than with azithromycin plus rifabutin (low-quality evidence).

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits:**Azithromycin versus placebo:**

One double-blind RCT (174 people with AIDS and CD4 count less than 100/mm³) found that azithromycin significantly reduced the incidence of *Mycobacterium avium* complex (MAC) at 30 days after completion of treatment compared with placebo (9/85 [11%] with azithromycin v 22/89 [25%] with placebo; P = 0.004).^[20] The RCT found no significant difference in all-cause mortality between groups but was underpowered to detect a clinically important difference in this outcome (at 12 months: 16% with azithromycin v 22% with placebo; reported as not significant, absolute numbers not reported).

Azithromycin versus rifabutin or versus azithromycin plus rifabutin:

We found one RCT, which compared three treatments: azithromycin alone, rifabutin alone, and azithromycin plus rifabutin.^[21] See benefits of macrolides plus rifabutin, p 13 .

Harms:**Azithromycin versus placebo:**

Gastrointestinal adverse effects were more likely with azithromycin than with placebo (71/90 [79%] with azithromycin v 25/91 [28%] with placebo; NNH 2, CI not reported), but they were rarely severe enough to cause discontinuation of treatment (8% with azithromycin v 2% with placebo; P = 0.14).^[20]

Azithromycin versus rifabutin or versus azithromycin plus rifabutin:

See harms of macrolides plus rifabutin, p 13 .

Comment:

Prospective cohort studies found that the risk of disseminated MAC disease increased substantially with a lower CD4 count and was clinically important only for CD4 counts less than 50/mm³.^[1]

Clinical guide:**Role of highly active antiretroviral treatment (HAART):**

Most of the RCTs of MAC prophylaxis were conducted before the widespread use of HAART. HAART reduces the absolute risk of MAC infection. The absolute risk reduction of prophylactic regimens may be smaller when used in people treated with HAART.

OPTION	CLARITHROMYCIN FOR PRIMARY PROPHYLAXIS FOR MYCOBACTERIUM AVIUM COMPLEX (MAC)
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Mycobacterium avium complex (MAC)

Clarithromycin compared with placebo Primary prophylaxis with clarithromycin is more effective at reducing the incidence of MAC at a mean of 10 months in people with advanced AIDS ([high-quality evidence](#)).

Clarithromycin alone compared with rifabutin alone or compared with clarithromycin plus rifabutin Primary prophylaxis with clarithromycin alone or clarithromycin plus rifabutin seems more effective than rifabutin alone at reducing the incidence of MAC in people with AIDS, but we don't know whether clarithromycin alone is more effective than clarithromycin plus rifabutin ([moderate-quality evidence](#)).

Mortality

Clarithromycin compared with placebo Primary prophylaxis with clarithromycin seems more effective at reducing all-cause mortality in people with advanced AIDS ([moderate-quality evidence](#)).

Clarithromycin alone compared with rifabutin alone or compared with clarithromycin plus rifabutin Primary prophylaxis with clarithromycin alone, clarithromycin plus rifabutin, and rifabutin alone seems equally effective at reducing all-cause mortality in people with AIDS ([moderate-quality evidence](#)).

Adverse effects

Clarithromycin alone compared with rifabutin alone or compared with clarithromycin plus rifabutin Primary prophylaxis with clarithromycin alone or rifabutin alone may be associated with a decrease in the proportion of people who have adverse effects compared with clarithromycin plus rifabutin ([low-quality evidence](#)).

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see [GRADE table, p 30](#).

Benefits:**Clarithromycin versus placebo:**

We found one systematic review (search date 1997) of prophylaxis and treatment of *Mycobacterium avium* complex (MAC).^[22] It identified one double-blind RCT (682 people with advanced AIDS),^[23] which found that clarithromycin significantly reduced the incidence of MAC over a mean 10.5 months compared with placebo (19/333 [6%] with clarithromycin v 53/334 [16%] with placebo; adjusted HR to allow for shorter (9.5 months) follow-up of people taking placebo 0.31, 95% CI 0.18 to 0.53). The RCT also found that clarithromycin significantly reduced all-cause mortality compared with placebo (107/333 [32%] with clarithromycin v 137/334 [41%] with placebo; HR 0.75, 95% CI 0.58 to 0.97; P = 0.03).^[23]

Clarithromycin versus rifabutin or versus clarithromycin plus rifabutin:

We found one RCT comparing three treatments: clarithromycin alone, rifabutin alone, and clarithromycin plus rifabutin.^[24] See [benefits macrolides plus rifabutin, p 13](#).

Harms:**Clarithromycin versus placebo:**

Adverse effects led to discontinuation of treatment in a slightly larger proportion of people taking clarithromycin than placebo (8% with clarithromycin v 6% with placebo; P = 0.45). Proportionately more people taking clarithromycin suffered altered taste or rectal disorders (altered taste: 11% with clarithromycin v 2% with placebo; rectal disorders: 8% with clarithromycin v 3% with placebo).^[20]

Clarithromycin versus rifabutin or versus clarithromycin plus rifabutin:

See [harms of macrolides plus rifabutin, p 13](#).

Comment:

Prospective cohort studies found that the risk of disseminated MAC disease increased substantially with a lower CD4 count and was clinically important only for CD4 counts less than 50/mm³.^[1] See [role of highly active antiretroviral treatment in comment on azithromycin, p 12](#).

OPTION	MACROLIDES PLUS RIFABUTIN VERSUS EITHER ALONE FOR PRIMARY PROPHYLAXIS FOR MYCOBACTERIUM AVIUM COMPLEX (MAC)
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Mycobacterium avium complex (MAC)

Clarithromycin plus rifabutin compared with clarithromycin alone or compared with rifabutin alone Primary prophylaxis with clarithromycin plus rifabutin or clarithromycin alone seems more effective than rifabutin alone at reducing the incidence of MAC in people with AIDS, but we don't know whether clarithromycin plus rifabutin is more effective than clarithromycin alone ([moderate-quality evidence](#)).

Azithromycin plus rifabutin compared with azithromycin alone or compared with rifabutin alone Primary prophylaxis with azithromycin plus rifabutin seems more effective than azithromycin alone or rifabutin alone at reducing the inci-

dence of MAC at 1 year in HIV-positive people. Primary prophylaxis with azithromycin alone seems more effective than rifabutin alone at reducing the incidence of MAC at 1 year in HIV-positive people (moderate-quality evidence).

Mortality

Clarithromycin plus rifabutin compared with clarithromycin alone or compared with rifabutin alone Primary prophylaxis with clarithromycin plus rifabutin, clarithromycin alone, and rifabutin alone seems equally effective reducing all-cause mortality in people with AIDS (moderate-quality evidence).

Azithromycin plus rifabutin compared with azithromycin alone or compared with rifabutin alone Primary prophylaxis with azithromycin plus rifabutin, azithromycin alone, or rifabutin alone seems equally effective at reducing all cause mortality in HIV-positive people (moderate-quality evidence).

Adverse effects

Clarithromycin plus rifabutin compared with clarithromycin alone or compared with rifabutin alone Primary prophylaxis with clarithromycin plus rifabutin may be associated with an increase in the proportion of people who have adverse effects compared with clarithromycin alone or rifabutin alone (low-quality evidence).

Azithromycin plus rifabutin compared with azithromycin alone or compared with rifabutin alone Dose-limiting toxicity may be more likely with azithromycin plus rifabutin than with azithromycin alone (low-quality evidence).

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits:

Clarithromycin plus rifabutin versus clarithromycin alone or versus rifabutin alone:

We found one double-blind RCT (1178 people with AIDS), which compared three interventions: clarithromycin plus rifabutin, clarithromycin alone, or rifabutin alone. ^[24] It found no significant difference in the risk of *Mycobacterium avium* complex (MAC) between the combination and clarithromycin alone (RR 0.79, 95% CI 0.48 to 1.31 for combination v clarithromycin; P = 0.36). It found that both the combination treatment and clarithromycin alone significantly reduced the risk of MAC compared with rifabutin alone (RR 0.43, 95% CI 0.27 to 0.69; P = 0.0003 for combination v rifabutin; RR 0.56, 95% CI 0.37 to 0.84; P = 0.005 for clarithromycin alone v rifabutin). The RCT found no significant difference in all-cause mortality between combination treatment and clarithromycin alone or rifabutin alone or between clarithromycin alone and rifabutin alone (RR 0.89, 95% CI 0.72 to 1.10 for combination v clarithromycin; P = 0.79; RR 0.92, 95% CI 0.74 to 1.13; P = 0.42 for combination v rifabutin; RR 0.97, 95% CI 0.78 to 1.20; P = 0.79 for clarithromycin alone v rifabutin).

Azithromycin plus rifabutin versus azithromycin alone or versus rifabutin alone:

One double-blind RCT (693 HIV-positive people) found that the combination of azithromycin plus rifabutin compared with azithromycin alone or rifabutin alone reduced the incidence of MAC at 1 year (15% with rifabutin v 8% with azithromycin v 3% with rifabutin plus azithromycin; P less than 0.001 for combination v rifabutin; P = 0.03 for combination v azithromycin). ^[21] Azithromycin alone also significantly reduced the incidence of MAC at 1 year compared with rifabutin alone (P = 0.008). There was similar all-cause mortality in all groups over the study period (median 514 days' follow-up: 81/224 [36%] with combination v 83/233 [37%] with azithromycin alone v 81/236 [34%] with rifabutin alone; significance not assessed).

Harms:

Rifabutin plus clarithromycin versus rifabutin alone or clarithromycin alone:

The RCT found that adverse events occurred in 31% of people receiving the combination of clarithromycin plus rifabutin compared with 16% with clarithromycin alone and 18% with rifabutin alone (P less than 0.001). ^[24] Uveitis occurred in 42 people: 33 with clarithromycin plus rifabutin, seven with rifabutin alone, and two with clarithromycin alone.

Uveitis:

We found one systematic review of case reports (search date 1994, 54 people with rifabutin-associated uveitis). ^[25] It found that uveitis was dose dependent. It occurred from 2 weeks to more than 7 months after initiation of rifabutin treatment, and was more likely in people taking rifabutin plus clarithromycin. In most people, uveitis resolved 1 to 2 months after discontinuation of rifabutin.

Rifabutin plus azithromycin versus rifabutin alone or azithromycin alone:

One RCT found that dose-limiting toxicity was more likely with azithromycin plus rifabutin compared with azithromycin alone (HR 1.67; P = 0.03). ^[21]

Comment:

Prospective cohort studies found that the risk of disseminated MAC disease increased substantially with a lower CD4 count and was clinically important only for CD4 counts less than 50/mm³. ^[1] Clarithromycin may inhibit rifabutin metabolism; rifabutin may decrease levels of delavirdine and saquinavir. See role of highly active antiretroviral treatment in comment on azithromycin, p 12 .

QUESTION What are the effects of secondary prophylaxis for disseminated *Mycobacterium avium* complex (MAC) disease in people with HIV infection and previous MAC disease?

OPTION **MACROLIDES PLUS ETHAMBUTOL FOR SECONDARY PROPHYLAXIS FOR MYCOBACTERIUM AVIUM COMPLEX (MAC)**

Mycobacterium avium complex (MAC)

Clarithromycin plus ethambutol compared with clarithromycin plus ethambutol plus rifabutin We don't know how secondary prophylaxis with clarithromycin plus ethambutol compares with clarithromycin plus ethambutol plus rifabutin at reducing rates of MAC ([very low-quality evidence](#)).

Mortality

Clarithromycin plus ethambutol compared with clarithromycin plus ethambutol plus rifabutin Secondary prophylaxis with clarithromycin plus ethambutol may be less effective at reducing all-cause mortality ([very low-quality evidence](#)).

Note

There is consensus that clarithromycin plus ethambutol is effective for secondary prophylaxis of MAC. We found no direct information from RCTs about the effects of azithromycin plus ethambutol.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see [GRADE table, p 30](#).

Benefits:

Clarithromycin plus ethambutol versus clarithromycin plus ethambutol plus rifabutin:

We found one RCT (160 people, open-label design) comparing three interventions: clarithromycin plus ethambutol, clarithromycin plus rifabutin, or all three drugs.^[26] It found no significant difference among groups in the proportion of people with microbiological and clinical response at 12 weeks (14/53 [26%] with clarithromycin plus ethambutol v 13/50 [26%] with clarithromycin plus rifabutin v 17/57 [30%] with all three drugs; $P = 0.9$). It found no significant difference in relapse rates between the combination of all three drugs and clarithromycin plus ethambutol (proportion who relapsed: 7% with clarithromycin plus ethambutol v 6% with all 3 drugs; $P = 0.6$, absolute numbers not reported). It found that the combination of all three drugs significantly reduced relapse over 48 weeks in those who had responded compared with clarithromycin plus rifabutin (proportion who relapsed: 24% with clarithromycin plus rifabutin v 6% with all 3 drugs; $P = 0.03$, absolute numbers not reported). It also found that the combination of all three drugs significantly increased survival at 48 weeks compared with either two-drug combination (HR 0.44, 95% CI 0.23 to 0.83 for all 3 drugs v clarithromycin plus ethambutol; HR 0.49, 95% CI 0.26 to 0.92 for all 3 drugs v clarithromycin plus rifabutin, absolute numbers not reported). These differences in survival remained significant when adjustments for protease inhibitor use and other prognostic factors were made.

Azithromycin plus ethambutol:

We found no RCTs.

Harms:

Combinations of drugs may lead to increased toxicity. Optic neuropathy may occur with ethambutol, but has not been reported in RCTs in people with HIV, where the dose and symptoms were carefully monitored.

Clarithromycin plus ethambutol versus clarithromycin plus ethambutol plus rifabutin:

The RCT found no significant difference among groups in the proportion of people who withdrew owing to adverse effects (7/53 [13%] with clarithromycin plus ethambutol v 12/50 [24%] with clarithromycin plus rifabutin v 8/57 [14%] with all 3 drugs; $P = 0.3$).^[26] Adverse effects were primarily gastrointestinal.

Azithromycin plus ethambutol:

We found no RCTs.

Higher-dose versus lower-dose clarithromycin:

One open-label RCT (85 people), which compared clarithromycin 500 mg twice daily versus 1000 mg twice daily, found that, after a median follow-up of 4.5 months, mortality was significantly higher with the higher dose (85 people; 17/40 [43%] with 1000 mg twice daily v 10/45 [22%] with 500 mg twice daily; ARI 20%, 95% CI 0.2% to 33%; NNH 5, 95% CI 3 to 470).^[27] A similar difference was seen in another double-blind RCT (154 people).^[28]

Comment:

Clinical guide:

Prospective cohort studies found that the risk of disseminated MAC disease increased substantially with a lower CD4 count and was clinically important only for CD4 counts less than $50/\text{mm}^3$.^[23] Clarithromycin may inhibit rifabutin metabolism; rifabutin may decrease levels of delavirdine and

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saquinavir. Although the combination of all three drugs showed survival benefit over a two-drug combination in one RCT, in the era of highly active antiretroviral treatment (HAART), most clinicians prescribe clarithromycin plus ethambutol because of toxicity and drug interactions with rifabutin.

QUESTION What are the effects of secondary prophylaxis for cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella zoster virus (VZV) in people with HIV infection?

OPTION ACICLOVIR FOR SECONDARY PROPHYLAXIS FOR HSV OR VZV

Herpes simplex virus (HSV), varicella zoster virus (VZV)

Aciclovir compared with valaciclovir Secondary prophylaxis with aciclovir or valaciclovir may be equally effective at reducing recurrence of HSV at 48 weeks in CMV-seropositive people with CD4 count greater than 100/mm³ (moderate-quality evidence).

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: **Aciclovir versus placebo:**
We found no systematic review or RCTs.

Aciclovir versus valaciclovir:

We found one double-blind RCT (1062 HIV-positive people with history of recurrent genital or anogenital HSV, and a median CD4 count of 320/mm³) compared aciclovir (400 mg twice daily) versus valaciclovir (500 mg twice daily or 1000 mg once daily).^[29] It found no significant difference between aciclovir and either dose of valaciclovir in HSV recurrence at 48 weeks (valaciclovir 500 mg twice daily v aciclovir: HR for recurrence 0.73, 95% CI 0.50 to 1.06; valaciclovir 1000 mg daily v aciclovir: HR for recurrence 1.31, 95% CI 0.94 to 1.82; absolute results presented graphically).^[29] The RCT did not assess differences between groups in all-cause mortality.

Harms: **Aciclovir versus placebo:**
We found no RCTs.

Aciclovir versus valaciclovir:

The second RCT found a similar frequency of adverse events (including headache and nausea) with aciclovir (400 mg twice daily) and valaciclovir (500 mg twice daily or 1000 mg once daily; AR for treatment limiting adverse events: 11% with valaciclovir [dose regimens pooled] v 9% with aciclovir; significance assessment not performed).^[29]

Comment: The survival benefit with aciclovir and valaciclovir is unclear. The absolute risk reduction may be higher in people who have frequent HSV or VZV infections. Aciclovir is no longer used as prophylaxis for CMV.

OPTION GANCICLOVIR FOR SECONDARY PROPHYLAXIS FOR CMV, HSV, OR VZV

We found no clinically important results from RCTs about the effects of ganciclovir for secondary prophylaxis against CMV, HSV, or VZV.

Note

There is consensus, based on the benefits of aciclovir in this population and clinical experience of use of ganciclovir, that ganciclovir is effective as secondary prophylaxis for CMV, HSV, or VZV.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: **Clinical guide:**
There is consensus, based on the benefits of aciclovir in people with HSV or VZV, and clinical experience of use of ganciclovir, that ganciclovir is effective as secondary prophylaxis for CMV, HSV, or VZV. Ganciclovir is currently used in preference to aciclovir, valaciclovir, or famciclovir for primary prophylaxis of CMV.

OPTION

VALACICLOVIR FOR SECONDARY PROPHYLAXIS FOR HSV OR VZV

Herpes simplex virus (HSV), varicella zoster virus (VZV)

Valaciclovir compared with placebo Secondary prophylaxis with valaciclovir seems more effective at reducing genital and oral HSV infection at 6 months in HIV-positive people with history of recurrent genital herpes and a median CD4 count of 313/mm³ to 336/mm³ (moderate-quality evidence).

Different valaciclovir dosage schedules compared with each other Secondary prophylaxis with valaciclovir 500 mg twice daily seems more effective than valaciclovir 1000 mg once daily at reducing anogenital HSV at 48 weeks in HIV-positive people with history of recurrent genital or anogenital HSV and a median CD4 count of 320/mm³ (moderate-quality evidence).

Valaciclovir compared with aciclovir Secondary prophylaxis with valaciclovir or aciclovir may be equally effective at reducing the incidence of HSV disease at 48 weeks in CMV-seropositive people with CD4 count less than 100/mm³ (moderate-quality evidence).

Note

Valaciclovir has been associated with increased risk of anaemia and neutropenia.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits:**Valaciclovir versus placebo:**

We found one double-blind RCT (293 HIV-positive people with history of recurrent genital herpes; median CD4 count 336/mm³ in the valaciclovir group and 313/mm³ in the placebo group) comparing valaciclovir 500 mg twice daily versus placebo.^[30] It found that valaciclovir significantly reduced genital herpes simplex virus (HSV) recurrence compared with placebo at 6 months (AR for being genital HSV-recurrence free: 65% with valaciclovir v 26% with placebo; RR 2.5, 95% CI 1.8 to 3.5). There was a significant reduction in oral herpes with valaciclovir compared with placebo at 6 months (AR for being oral HSV-recurrence-free: 76% with valaciclovir v 62% with placebo; RR 1.24, 95% CI 1.04 to 1.48). The RCT did not assess all-cause mortality.

Different valaciclovir dosage schedules:

We found one double-blind RCT comparing three treatments: valaciclovir 500 mg twice daily, valaciclovir 1000 mg once daily, and aciclovir 400 mg twice daily.^[29] It found that valaciclovir 500 mg twice daily significantly reduced anogenital HSV recurrence at 48 weeks compared with valaciclovir 1000 mg daily (HR 0.56, 95% CI 0.39 to 0.79; absolute results presented graphically). The RCT did not assess differences between groups in all-cause mortality.^[29]

Valaciclovir versus aciclovir:

See benefits of aciclovir, p 17 .

Harms:**Valaciclovir versus placebo:**

The RCT found that valaciclovir increased the risk of adverse effects (including headache, diarrhoea, fatigue, and nausea) compared with placebo (overall adverse effects: 75% with valaciclovir v 58% with placebo; significance assessment not performed).^[30]

Different valaciclovir dosage schedules:

Adverse effects were similar with the different dosage schedules (diarrhoea: 19% with valaciclovir 500 mg twice daily v 21% with valaciclovir 1000 mg once daily; headache: 18% in each group; significance assessment not performed).

Valaciclovir versus aciclovir:

See harms of aciclovir, p 16 .

Comment:

Valaciclovir is associated with anaemia and neutropenia.

OPTION

FAMCICLOVIR FOR SECONDARY PROPHYLAXIS FOR HSV OR VZV

Herpes simplex virus (HSV), varicella zoster virus (VZV)

Famciclovir compared with placebo Secondary prophylaxis with famciclovir may be more effective at suppressing viral shedding of HSV in people with frequent recurrences, but we don't know about clinical outcomes (very low-quality evidence).

Note

There is consensus, based on the benefits of aciclovir in people with HSV or VZV, and clinical experience of use of famciclovir, that famciclovir is effective as secondary prophylaxis for HSV or VZV.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits:**Famciclovir versus placebo:**

We found no systematic review. One double-blind crossover placebo-controlled RCT (48 people) found that secondary famciclovir suppressed viral shedding of herpes simplex virus (HSV) in people with frequent recurrences (in an intention-to-treat analysis before crossover HSV was isolated in 9/1071 [1%] famciclovir days v 122/1114 [11%] placebo days; P less than 0.001).^[31] Breakthrough reactivations on famciclovir were short lived and often asymptomatic. The RCT did not assess all-cause mortality.

Harms:**Famciclovir versus placebo:**

Famciclovir was well tolerated, and the incidence of adverse effects was similar in both groups.^[31]

Comment:

The conclusions of this RCT are difficult to interpret. The randomisation process allocated participants to groups, but the intention-to-treat analysis involved the number of days with symptoms rather than the number of participants who improved. There was no assessment of statistical significance of clinical outcomes. The analysis of the trial was impeded by a high withdrawal rate. There is consensus, based on the benefits of aciclovir in people with HSV or VZV, and clinical experience of use of famciclovir, that famciclovir is effective as secondary prophylaxis for HSV or VZV.

QUESTION

What are the effects of primary prophylaxis for invasive fungal disease in people with HIV infection without previous fungal disease?

OPTION

AZOLES FOR PRIMARY PROPHYLAXIS FOR INVASIVE FUNGAL DISEASE

Invasive fungal disease

Fluconazole compared with placebo We don't know whether primary prophylaxis with fluconazole is more effective at reducing the incidence of invasive cryptococcal disease at 4.7 months in people in Thailand with CD4 counts less than 100/mm³ (very low-quality evidence).

Itraconazole compared with placebo Primary prophylaxis with itraconazole is more effective at reducing the incidence of invasive fungal disease at 16 months in people in both developed and developing countries with CD4 counts ranging from less than 300/mm³ to less than 100/mm³ (high-quality evidence).

High-dose fluconazole compared with low-dose fluconazole We don't know how primary prophylaxis with fluconazole 200 mg daily compares with fluconazole 400 mg once weekly at reducing the rate of invasive fungal infections over 74 weeks (low-quality evidence).

Fluconazole compared with clotrimazole troches Primary prophylaxis with fluconazole may be more effective at reducing the incidence of invasive fungal infections at 35 months in people in the US with CD4 counts less than 200/mm³ (low-quality evidence).

Mortality

Fluconazole compared with placebo We don't know whether fluconazole is more effective at reducing all-cause mortality at 4.7 months in people in Thailand with CD4 counts less than 100/mm³ (very low-quality evidence).

Itraconazole compared with placebo Primary prophylaxis with itraconazole seems no more effective at reducing all-cause mortality at 16 months in people in both developed and developing countries with CD4 counts ranging from less than 300/mm³ to less than 100/mm³ (high-quality evidence).

High-dose fluconazole compared with low-dose fluconazole We don't know how primary prophylaxis with fluconazole 200 mg daily compares with fluconazole 400 mg once weekly at reducing all-cause mortality over 74 weeks (low-quality evidence).

Fluconazole compared with clotrimazole troches We don't know how primary prophylaxis with fluconazole compares with clotrimazole troches at reducing all-cause mortality at 35 months in people in the US with CD4 counts less than 200/mm³ (low-quality evidence).

Note

Azoles have been associated with congenital anomalies and potentially serious interactions with other drugs.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits:**Fluconazole versus placebo:**

We found one systematic review (search date 2004), which identified one double-blind RCT (90 people in Thailand with CD4 counts less than 100/mm³) comparing fluconazole versus placebo.^[32] The RCT found no significant difference between fluconazole and placebo in the incidence of invasive cryptococcal disease over a median 4.7 months, but it may have lacked power to detect a clinically important difference between groups (3/44 [7%] with fluconazole v 7/46 [15%] with placebo; RR 0.45, 95% CI 0.12 to 1.62). The RCT also found no significant difference between fluconazole and placebo in all-cause mortality over a median 4.7 months, but it may have lacked power to detect a clinically important difference between groups (2/44 [5%] with fluconazole v 9/46 [20%] with placebo; RR 0.23, 95% CI 0.05 to 1.02).^[32]

Itraconazole versus placebo:

We found one systematic review (search date 2004), which identified three double-blind RCTs (798 people in both developed and developing countries with CD4 counts ranging from less than 300/mm³ to less than 100/mm³) comparing itraconazole versus placebo.^[32] The review found that itraconazole significantly reduced the incidence of invasive fungal infections over about 16 months (1/399 [0.3%] with itraconazole v 17/399 [2%] with placebo; RR 0.12, 95% CI 0.03 to 0.51). However, the review found no significant difference in all-cause mortality over about 16 months between itraconazole and placebo (53/399 [13%] with itraconazole v 46/399 [11%] with placebo; RR 1.12, 95% CI 0.70 to 1.80).

High-dose versus low-dose fluconazole:

One double-blind multicentre RCT (636 people) compared fluconazole 200 mg daily versus 400 mg once weekly and found no significant difference in the rate of invasive fungal infections over a follow-up of 74 weeks (8% with 200 mg daily v 6% with 400 mg once weekly; ARR +2.2%, 95% CI -1.7% to +6.0%).^[33] The RCT found no significant difference between groups in all-cause mortality at 74 weeks (36.7% with 200 mg daily v 37.2% with 400 mg once weekly; HR 0.98, 95% CI 0.76 to 1.26).

Fluconazole versus clotrimazole troches:

We found one systematic review (search date 2004),^[32] which identified one open-label RCT^[34] (428 people in the US with CD4 counts less than 200/mm³) comparing fluconazole 200 mg daily versus clotrimazole troches 10 mg five times daily. The RCT found that fluconazole 200 mg daily significantly reduced the incidence of invasive fungal infections compared with clotrimazole troches (10 mg 5 times/day) after a median follow-up of 35 months (4% with fluconazole v 11% with clotrimazole; HR of developing infection 3.3, 95% CI 1.5 to 7.6).^[34] The RCT found no significant difference between groups in all-cause mortality, but it may have been underpowered to detect a clinically important difference between groups (98/217 [45%] with fluconazole v 89/211 [42%] with clotrimazole; HR for death 0.9, 95% CI 0.6 to 1.1; P = 0.26).

Harms:

Congenital anomalies have occurred in a few children born to mothers receiving fluconazole. Itraconazole is embryotoxic and teratogenic in animals. Trials have therefore excluded pregnant women. Azoles may interact with antiretroviral regimens, although the effects tend to be modest and most do not require dose adjustments.^[35] Azoles inhibit the metabolism of some drugs such as terfenadine. Theoretically they may increase the risk of sudden death due to ventricular tachycardia.

Fluconazole versus placebo:

The RCT identified by the review gave no information on adverse effects.^[32]

Itraconazole versus placebo:

The review reported that the data on adverse effects provided by the RCTs assessing itraconazole versus placebo were insufficient to perform any meaningful statistical analyses.^[32] The first RCT identified by the review found that itraconazole significantly increased the proportion of people with skin rash compared with placebo (10% with itraconazole v 2% with placebo; P = 0.02).^[36] The second RCT identified by the review found no significant difference between treatments in overall adverse effects, including skin rashes (skin rashes: 25% with itraconazole v 23% with placebo; overall adverse effects; P greater than 0.5).^[37] The third RCT identified by the review found a similar frequency of adverse effects in both treatment groups.^[38] It also found that early medication discontinuations were similar between treatment groups (20% with itraconazole v 23% with placebo).

High-dose versus low-dose fluconazole:

The RCT found that a similar proportion of people experienced gastrointestinal symptoms in both treatment groups (73% with 200 mg daily v 70% with 400 mg once weekly). It found that 3.1% of people in the fluconazole 200 mg-daily group and 2.5% of people in the fluconazole 400 mg once-weekly group withdrew from treatment because of adverse effects (increased liver function tests or haematological abnormalities).^[33]

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Fluconazole versus clotrimazole troches:

The RCT identified by the review ^[32] found a similar frequency of adverse effects in both treatment groups. It also found that fluconazole did not significantly increase the proportion of people who discontinued treatment compared with clotrimazole (13 people with fluconazole v 6 people with clotrimazole; $P = 0.11$). ^[34]

Comment:

Azoles effectively reduce invasive fungal disease. Any absolute benefit is probably even lower in people treated with highly active antiretroviral treatment. Lack of evidence of any survival benefit, potential for complex drug interactions with current antiretroviral regimens, and potential for developing resistant fungal isolates means that there is doubt about routine antifungal prophylaxis in HIV-infected people without previous invasive fungal disease, although one large open-label RCT (829 people with oral candidiasis) found no significant difference in rates of fluconazole-resistant infections over 42 months between continuous and episodic fluconazole (proportion of people with azole-resistant candidiasis: 17/413 [4.1%] with continuous v 18/416 [4.3%] with episodic prophylaxis; $P = 0.88$). ^[39]

QUESTION

What are the effects of secondary prophylaxis for invasive fungal disease in people with HIV infection and previous invasive fungal disease?

OPTION

AZOLES FOR SECONDARY PROPHYLAXIS FOR *PENICILLIUM MARNEFFEI*

Penicillium marneffei

Itraconazole compared with placebo Secondary prophylaxis with itraconazole seems more effective at reducing the relapse of *Penicillium marneffei* infection in people with AIDS in Asia ([moderate-quality evidence](#)).

Mortality

Itraconazole compared with placebo We don't know whether secondary prophylaxis with itraconazole is more effective at reducing all-cause mortality in people with AIDS in Asia ([moderate-quality evidence](#)).

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see [GRADE table, p 30](#).

Benefits:

We found no systematic review.

Itraconazole versus placebo:

We found one double-blind RCT (71 people with AIDS in Asia), which found that itraconazole significantly reduced the relapse of *Penicillium marneffei* infection compared with placebo (AR for relapse within 1 year: 0/36 [0%] with itraconazole v 20/35 [57%] with placebo; P less than 0.001). ^[40] The RCT found no significant difference between groups in all-cause mortality, but it may have been underpowered to detect a clinically important difference (11/36 [31%] with itraconazole v 15/35 [43%] with placebo; $P = 0.27$).

Fluconazole:

We found no systematic review or RCTs.

Harms:**Itraconazole versus placebo:**

The RCT gave no information on adverse effects. ^[40]

Fluconazole:

We found no RCTs.

Comment:**Clinical guide:**

Recurrent infection is common in people with previous *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Penicillium marneffei* infections. Lifelong maintenance may be needed in the presence of immune impairment, but it appears safe to discontinue in the setting of immune reconstitution.

OPTION

AZOLES FOR SECONDARY PROPHYLAXIS FOR CRYPTOCOCCAL MENINGITIS

Cryptococcal meningitis

Itraconazole compared with fluconazole Secondary prophylaxis with itraconazole is less effective in reducing relapses of successfully treated cryptococcal meningitis over 12 months in people with HIV infection ([high-quality evidence](#)).

Mortality

Itraconazole compared with fluconazole We don't know how secondary prophylaxis with itraconazole compares with fluconazole at reducing all-cause mortality in people with HIV infection ([low-quality evidence](#)).

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: We found no systematic review.

Itraconazole versus fluconazole:

One double-blind RCT (108 people with HIV infection) found that fluconazole significantly reduced relapses of successfully treated cryptococcal meningitis over 12 months compared with itraconazole (AR for relapse: 13/57 [23%] with itraconazole v 2/51 [4%] with fluconazole; ARR 19.0%, 95% CI 6.2% to 31.7%; RR 0.17, 95% CI 0.04 to 0.71; NNT 5, 95% CI 3 to 16).^[41] The trial was stopped early because of the higher rate of relapse with itraconazole. It found no significant difference in all-cause mortality between groups (6/57 [10%] with itraconazole v 8/51 [16%] with fluconazole; P = 0.81).

Harms: The RCT reported that two people discontinued itraconazole because of skin rashes, one discontinued because of severe anaemia, and one discontinued because of gastrointestinal effects, compared with no discontinuations in people taking fluconazole.^[41]

Comment: **Clinical guide:** Recurrent infection is common in people with previous *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *P. marneffei* infections. Lifelong maintenance may be needed in the presence of immune impairment but it appears safe to discontinue in the setting of immune reconstitution.

QUESTION What are the effects of discontinuing primary prophylaxis against opportunistic pathogens in people with HIV infection taking highly active antiretroviral treatment (HAART)?

OPTION DISCONTINUING PRIMARY PROPHYLAXIS FOR P JIROVECI PNEUMONIA (PCP) AND TOXOPLASMOSIS

Pneumocystis jirovecii pneumonia (PCP)

Discontinuation compared with continuation of primary prophylaxis Discontinuing primary prophylaxis for PCP does not seem to increase rates of PCP at 20 months in adults aged over 18 years with HIV and an increase of CD4 cell count to greater than 200/mm³ for at least 3 months after taking highly active antiretroviral treatment (HAART) (moderate-quality evidence).

Toxoplasmosis

Discontinuation compared with continuation of primary prophylaxis Discontinuing primary prophylaxis for toxoplasmosis may not increase rates toxoplasma encephalitis at 6 months or toxoplasmosis at 12 months in adults aged over 18 years with HIV and an increase of CD4 cell count to greater than 200/mm³ for at least 3 months after taking HAART (low-quality evidence).

Note

In the RCTs, in all participants randomised to discontinuation, prophylaxis was re-started if CD4 counts fell below 200/mm³.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: ***Pneumocystis jirovecii pneumonia (PCP):*** We found one systematic review (search date 2001),^[42] which identified one open-label RCT comparing discontinuation versus continuation of either primary or secondary prophylaxis (primarily trimethoprim-sulfamethoxazole) for PCP.^[43] In people who had been receiving primary prophylaxis (474 adults aged over 18 years with HIV from 19 Spanish hospitals and an increase of CD4 cell count to greater than 200/mm³ for at least 3 months after taking highly active antiretroviral treatment [HAART]), there were no episodes of PCP in either group after a median follow-up of 20 months; in all participants randomised to discontinuation, prophylaxis was re-started if CD4 counts fell below 200/mm³. None of the participants was lost to follow-up.

Toxoplasmosis:

We found one systematic review (search date 2001),^[42] which identified two RCTs,^[44] ^[45] one of which^[45] was published only as abstract at the time of the review.

The first RCT identified by the review found no cases of *Toxoplasma* encephalitis at 6 months in people discontinuing prophylaxis.^[44]

The second RCT identified by the review, later published in full, was open label and compared discontinuation versus continuation of either primary or secondary prophylaxis (prophylaxis not

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specified) for toxoplasmic encephalitis. ^[46] In people who had been receiving primary prophylaxis (381 adults aged over 18 years with HIV from 22 Spanish hospitals, no history of toxoplasmosis, and an increase of CD4 cell count to greater than 200/mm³ for at least 3 months after taking HAART), there were no episodes of toxoplasmosis in either group at 12 months; in all participants randomised to discontinuation, prophylaxis was re-started if CD4 counts fell below 200/mm³. None of the participants was lost to follow-up.

Harms: The review found no direct harms from discontinuing prophylaxis. ^[42]

Comment: The review performed a meta-analysis about the effects of discontinuing prophylaxis including the two RCTs plus two non-randomised controlled trials and 10 studies with other designs (3584 people, 3035 discontinuing primary prophylaxis, 549 discontinuing secondary prophylaxis). ^[42] The review found a low incidence of PCP in people discontinuing both primary and secondary prophylaxis after a mean of 1.5 years (7/3035 [0.23%] with discontinuing primary prophylaxis v 1/549 [0.18%] with discontinuing secondary prophylaxis; mean annual incidence over 1.5 years 0.23%, 95% CI 0.10% to 0.46%; no statistical heterogeneity among studies).

Clinical guide:

The risk of PCP may increase after discontinuing prophylaxis in people who do not respond to antiretroviral treatment. We found no direct evidence of the effects of different HAART regimens on the risk of PCP or toxoplasmosis. Antiretroviral regimens with different mechanisms of action may have different clinical effects on opportunistic infections and HIV disease progression, despite inducing satisfactory suppression of HIV-1 replication and adequate CD4 responses. Also, CD4 cell count is an incomplete marker of immune reconstitution. It is possible that people with the same CD4 count may have different immune deficits regarding control of PCP and other opportunistic pathogens. An extensive amount of research is being conducted on other parameters of immune reconstitution, but the clinical implications are uncertain at present. One decision analysis based on the systematic review suggested that, in the long term, discontinuation of PCP prophylaxis in people who respond to HAART should result in fewer PCP episodes and fewer prophylaxis-related adverse effects. ^[42]

OPTION**DISCONTINUING PRIMARY PROPHYLAXIS FOR M AVIUM COMPLEX (MAC)****Mycobacterium avium complex (MAC)**

Discontinuation compared with continuation of primary prophylaxis Discontinuing primary prophylaxis with azithromycin for MAC does not seem to increase rates of MAC at 12 to 16 months in people with CD4 count greater than 100/mm³ in response to highly active antiretroviral treatment (HAART) (*moderate-quality evidence*).

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: We found two RCTs. ^[47] ^[48] The first RCT (520 people without previous *Mycobacterium avium* complex (MAC) disease, with CD4 count greater than 100/mm³ in response to highly active antiretroviral treatment [HAART]) compared azithromycin versus placebo. ^[47] It found no episodes of confirmed MAC disease in either group over a median follow-up of 12 months. The second RCT (643 people with CD4 count greater than 100/mm³ in response to HAART) compared azithromycin 1200 mg once weekly versus placebo. Over a median follow-up of 16 months there was no significant difference in the incidence of MAC between the groups (0/322 [0%] with azithromycin v 2/321 [1%] with placebo; difference +0.5 events/100 person-years, 95% CI -0.2 events/100 person-years to +1.2 events/100 person-years). ^[48]

Harms: In both RCTs, adverse effects leading to discontinuation of treatment were more common with azithromycin than with placebo (first RCT: 7% with azithromycin v 1% with placebo; P = 0.002; ^[47] second RCT: 8% with azithromycin v 2% with placebo; P less than 0.001). ^[48]

Comment: It is not clear whether different antiretroviral regimens have different clinical effects on opportunistic infections and on the need for specific prophylaxis.

OPTION**DISCONTINUING PRIMARY PROPHYLAXIS FOR INVASIVE FUNGAL DISEASE**

We found no clinically important results from RCTs about the effects of discontinuing primary prophylaxis for invasive fungal disease.

Note

Consensus suggests it may be safe to discontinue primary prophylaxis for invasive fungal disease among those who have had a CD4 count greater than 100/mm³ for at least 6 months while on highly active antiretroviral treatment (HAART).

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: There is consensus that primary prophylaxis can be discontinued in people who receive effective antiretroviral treatment and have sustained rises in CD4 counts (stable CD4 count of greater than 100/mm³ for at least 6 months).

QUESTION What are the effects of discontinuing secondary prophylaxis against opportunistic pathogens in people with HIV infection on highly active antiretroviral treatment (HAART)?

OPTION DISCONTINUING SECONDARY PROPHYLAXIS FOR PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP) OR TOXOPLASMOSIS New

Pneumocystis jirovecii pneumonia (PCP)

Discontinuation compared with continuation of secondary prophylaxis Discontinuing secondary prophylaxis for PCP does not seem to increase rates of PCP at 20 to 24 months in adults aged over 18 years with HIV and an increase of CD4 cell count to greater than 200/mm³ for at least 3 months after taking highly active antiretroviral treatment (HAART) (*moderate-quality evidence*).

Toxoplasmosis

Discontinuation compared with continuation of primary prophylaxis Discontinuing secondary prophylaxis for toxoplasmosis does not seem to increase rates of toxoplasma encephalitis at 12 months in adults aged over 18 years with HIV and an increase of CD4 cell count to greater than 200/mm³ for at least 3 months after taking HAART (*low-quality evidence*).

Note

In the RCTs, in all participants randomised to discontinuation, prophylaxis was re-started if CD4 counts fell below 200/mm³. RCT evidence is supported by multiple observational studies suggesting discontinuation is safe once the CD4 cell count has risen to greater than 200/mm³ on HAART. In people who developed PCP at a time with CD4 counts greater than 200/mm³, it is recommended that PCP prophylaxis be considered for life.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: ***Pneumocystis jirovecii pneumonia (PCP):***

We found one systematic review (search date 2001),^[42] which identified two open-label RCTs.^{[43] [49]} Neither found an increase in rates of PCP with discontinuation of secondary prophylaxis.

The first RCT compared discontinuation versus continuation of either primary or secondary prophylaxis (primarily trimethoprim–sulfamethoxazole [TMP-SMX; co-trimoxazole]) for PCP.^[43] In people who had been receiving secondary prophylaxis (113 adults aged over 18 years with HIV from 19 Spanish hospitals and a history of PCP and an increase of CD4 cell count to greater than 200/mm³ for at least 3 months after taking highly active antiretroviral treatment [HAART]), there were no episodes of PCP in either group after a median follow-up of 20 months; in all participants randomised to discontinuation, prophylaxis was re-started if CD4 counts fell below 200/mm³. None of the participants was lost to follow-up.

The second RCT (146 adults aged over 18 years with HIV in Italy and a history of PCP and an increase of CD4 cell count to greater than 200/mm³ for at least 3 months after taking HAART) compared discontinuation (77 people) versus continuation (69 people) of secondary prophylaxis for PCP (prophylaxis not specified).^[49] It found no significant difference in rates of PCP over 2 years (2 cases, both in people who had discontinued prophylaxis, incidence per 100 person-years: 4.3 with discontinuation v 2.7 with continuation; P = 0.30, intention-to-treat analysis). All participants randomised to discontinuation were offered the option to re-start prophylaxis if CD4 counts fell below 200/mm³ and were closely observed for the duration of the trial. None of the participants was lost to follow-up.

Toxoplasmosis:

We found one open-label RCT comparing discontinuation versus continuation of either primary or secondary prophylaxis (prophylaxis not specified) for toxoplasmic encephalitis. [46] In people who had been receiving secondary prophylaxis (57 adults aged over 18 years with HIV from 22 Spanish hospitals and a previous episode of toxoplasmosis and an increase of CD4 cell count to greater than 200/mm³ for at least 3 months after taking HAART), there were no episodes of toxoplasmosis in either group at 12 months; in all participants randomised to discontinuation, prophylaxis was restarted if CD4 counts fell below 200/mm³. All participants discontinued prophylaxis at 1 year and there were no episodes of toxoplasmosis over further follow-up over 2 years. None of the participants was lost to follow up.

Harms: None of the RCTs assessed adverse effects. [43] [49] [46]

Comment: **Clinical guide:**

The review performed a meta-analysis about the effects of discontinuing prophylaxis including two RCTs plus two non-randomised controlled trials and 10 studies with other designs (3584 people, 3035 discontinuing primary prophylaxis, 549 discontinuing secondary prophylaxis). [42] The review found a low incidence of PCP in people discontinuing both primary and secondary prophylaxis after a mean of 1.5 years (7/3035 [0.23%] with discontinuing primary prophylaxis v 1/549 [0.18%] discontinuing secondary prophylaxis; mean annual incidence over 1.5 years 0.23%, 95% CI 0.10% to 0.46%; no statistical heterogeneity among studies).

Overall, clinical experience suggests that discontinuing secondary prophylaxis seems safe without risk for relapse, and that it decreases pill burden, potential drug toxicity, drug interactions, and cost. In addition to the RCTs reported above, [43] [49] [46] discontinuation of secondary prophylaxis for PCP and toxoplasmosis once the CD4 cell count has risen to greater than 200/mm³ on HAART has been shown to be safe in multiple observational studies of which we reference a sample. [50] [51] [52] [53] In people who developed PCP at a time with CD4 counts greater than 200/mm³, it is recommended that PCP prophylaxis be considered for life.

OPTION**DISCONTINUING SECONDARY PROPHYLAXIS FOR CYTOMEGALOVIRUS**

New

We found no direct evidence from RCTs on the effects of discontinuing secondary prophylaxis for cytomegalovirus compared with continuing secondary prophylaxis in people who had responded to taking highly active antiretroviral treatment (HAART).

Note

Although we found no RCTs, there is consensus that discontinuation of secondary prophylaxis (chronic suppression) for CMV retinitis is safe to consider in people whose CD4 cell count is greater than 100/mm³ to 150/mm³ for more than 6 months and who had a non-sight-threatening lesion, adequate vision in the other eye, and the ability to undergo regular ophthalmological examinations. All people discontinuing prophylaxis should have regular fundoscopic monitoring to detect early recurrence and immune-reconstitution uveitis.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: **Clinical guide:**

Observational evidence suggest that discontinuation of secondary prophylaxis (chronic suppression) for CMV retinitis is safe to consider in people whose CD4 cell count is greater than 100 to 150/mm³ for more than 6 months and who had a non-sight-threatening lesion, adequate vision in the other eye, and the ability to undergo regular ophthalmological examinations. [54] [55] [56] [57] [58] [59] [60] [61] [62] For full details of case series see table 1, p 29 . All patients discontinuing prophylaxis should have regular fundoscopic monitoring to detect early recurrence and immune-reconstitution uveitis.

OPTION**DISCONTINUING SECONDARY PROPHYLAXIS FOR M AVIUM COMPLEX (MAC)**

New

We found no direct evidence from RCTs on the effects of discontinuing secondary prophylaxis for *Mycobacterium avium* complex (MAC) disease compared with continuing prophylaxis in people who had responded to taking highly active antiretroviral treatment (HAART).

Note

Consensus suggests it is safe to discontinue secondary prophylaxis for MAC among those who have completed at least 12 months of antimycobacterial therapy, are asymptomatic, and have had a CD4 count greater than 100/mm³ for at least 3 to 6 months on HAART. In people with increased CD4 counts on HAART who develop atypical manifestations of MAC, it may be prudent to treat for a prolonged period of 12 to 18 months and then continue chronic suppressive treatment for life.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: **Clinical guide:** It is safe to discontinue secondary prophylaxis for *Mycobacterium avium* complex (MAC) disease among those who have completed at least 12 months of antimycobacterial treatment, are asymptomatic, and have had a CD4 count greater than 100/mm³ for at least 3 to 6 months on HAART. Observational data suggest that, in most people with MAC who have received secondary prophylaxis for at least 12 months and have a CD4 count greater than 100/mm³, discontinuing prophylaxis does not lead to recurrence within 8 to 30 months.^{[63] [64] [50] [51] [53] [65]} However, atypical manifestations of MAC may occur in people having sustained elevations of CD4 T cells.^{[64] [50]} In people with increased CD4 counts on HAART who develop atypical manifestations of MAC, it may be prudent to treat for a prolonged period of 12 to 18 months and then continue chronic suppressive treatment for life.

OPTION

DISCONTINUING SECONDARY PROPHYLAXIS FOR INVASIVE FUNGAL DISEASE

New

Invasive fungal disease

Discontinuation compared with continuation of secondary prophylaxis Discontinuing secondary prophylaxis for cryptococcal meningitis does not seem to increase rates of cryptococcal meningitis at 48 weeks in people whose CD4 cell count had increased to greater than 100/mm³ and whose HIV RNA level had been undetectable for 3 months on potent antiretroviral treatment (*very low-quality evidence*).

Note

We found no RCTs on the effects of discontinuing secondary prophylaxis in other forms of invasive fungal disease.

For GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections, see GRADE table, p 30 .

Benefits: We found one RCT (60 people who had been successfully treated for acute cryptococcal meningitis), which randomised 42 people to continuation (22 people) versus discontinuation (20 people) of secondary prophylaxis when their CD4 cell count had increased to greater than 100/mm³ and HIV RNA level had been undetectable for 3 months when receiving zidovudine, lamivudine, and efavirenz.^[66] Pre-randomisation, the trial excluded 18 people owing to loss to follow-up (9 people), death (2 people), or failure to achieve CD4 count of greater than 100/mm³ (7 people). The RCT found that, at a median of 48 weeks after randomisation, there were no episodes of cryptococcal meningitis in either group (no further data reported).^[66]

Harms: The RCT gave no information on adverse effects.^[66]

Comment: **Clinical guide:** Discontinuation of secondary prophylaxis for cryptococcosis and histoplasmosis has been shown to be safe and effective in patients whose CD4 counts remain greater than 150 to 200/mm³ for at least 6 months. The RCT^[66] is supported by observational data, including two small prospective case series,^{[67] [68]} four small^{[69] [70] [71] [72]} and one larger (100 people who at the time maintenance therapy was discontinued had a median CD4 cell count of 259 cells and median plasma HIV viral load less than 2.30 log₁₀ copies/mL)^[73] retrospective studies, which found no recurrence of cryptococcosis in participants discontinuing secondary prophylaxis once they had responded to highly active antiretroviral treatment (HAART). A small prospective observational study (32 HIV-positive people) found no relapses of disseminated histoplasmosis at 24 months in people discontinuing secondary prophylaxis.^[74]

GLOSSARY

WHO staging system for HIV infection and disease consists of a "clinical axis" that is represented by a sequential list of clinical conditions believed to have prognostic significance, which subdivides the course of HIV infection into

four clinical stages; and a “laboratory axis” that subdivides each clinical stage into three strata according to CD4 cell count or total lymphocyte count.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Penicillium marneffei infection A common opportunistic infection in South East Asia.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Discontinuing secondary prophylaxis for PCP or toxoplasmosis New option for which we found three RCTs. [43] [49] [46] Categorised as Likely to be beneficial based both on RCTs and observational evidence.

Discontinuing secondary prophylaxis for CMV New option for which we found no RCTs. However, categorised as Likely to be beneficial as there is consensus that discontinuation is safe in people receiving highly active antiretroviral treatment (HAART) if the CD4 cell count is greater than 100 to 150/mm³ for more than 6 months and regular eye tests are undertaken.

Discontinuing secondary prophylaxis for MAC New option for which we found no RCTs. However, categorised as Likely to be beneficial as there is consensus that discontinuation is safe in people who have completed at least 12 months of antimycobacterial treatment, are asymptomatic, and have had a CD4 count greater than 100/mm³ for at least 3 to 6 months on highly active antiretroviral treatment (HAART).

Discontinuing secondary prophylaxis for invasive fungal disease New option for which we found one small RCT, [66] which found that, in people with stable CD4 count of greater than 100/mm³, there were no cases of cryptococcal meningitis over 1 year after secondary prophylaxis was discontinued. This is supported by observational evidence that discontinuation of secondary prophylaxis for cryptococcosis and histoplasmosis is safe and effective in people whose CD4 counts remain greater than 100 to 200/mm³ for at least 3 to 6 months. Categorised as Likely to be beneficial by consensus.

Antituberculosis prophylactic regimens versus placebo Two RCTs added. [15] [16] One RCT found no significant difference in rates of tuberculosis between isoniazid and placebo in people with HIV who were tuberculin skin negative. [15] The other RCT found that isoniazid reduced rates of tuberculosis compared with placebo in children, 85% of whom were tuberculin-skin negative but these results need to be interpreted with caution as the trial was terminated early. [16] Categorisation unchanged (Beneficial).

Azoles for primary prophylaxis for invasive fungal disease One systematic review added, which identified the same RCTs as those previously included in *Clinical Evidence*. [32] Categorisation unchanged (Trade-off between benefits and harms).

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Judith Aberg

Associate Professor of Medicine
Director of Virology
Bellevue Hospital Center, New York University School of Medicine
New York
USA

William Powderly

Professor of Medicine and Therapeutics
Dean
UCD School of Medicine and Medical Sciences, University College Dublin
Dublin
Ireland

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TABLE 1 Observational studies of discontinuation of secondary prophylaxis against cytomegalovirus maintenance treatment in people with previous cytomegalovirus disease.

Ref	Criteria for discontinuation	Participants	Follow up (months)	Relapses
[61]	CD4 greater than 70	17	14.5 (mean)	5
[57]	CD4 75 or greater	8	8 (median)	0
[62]	CD4 greater than 150	14	16.4 (mean)	0
[58]	CD4 greater than 100	8	11.4 (mean)	0
[59] *	CD4 183 (median)	11	5 (median)	0
[60]	CD4 greater than 150 VL less than 200/mL –ve CMV by PCR	7	9 (median)	0
[56]	CD4 greater than 75 VL less than 30,000/mL	48	11 (mean)	2
[55]	CD4 greater than 100 VL less than 500 or CD4 greater than 150 VL less than 10,000 copies/mL	36	21 (median)	1
[54]	CD4 greater than 143	41	20.4 (mean)	0

Studies with more than 5 people are included. CD4 count is measured in cells/mm³. * McDonald et al [59] is an early report of the same study followed by the Torriani et al [61] report. All relapses in the latter report occurred in people who had already experienced a decrease of CD4 to less than 50/mm³. CMV, cytomegalovirus; PCR, polymerase chain reaction; Ref, reference; VL, viral load (HIV-1 RNA in plasma); –ve, negative.

TABLE GRADE evaluation of interventions for HIV: primary and secondary prophylaxis for opportunistic infections

Important outcomes		<i>Pneumocystis jirovecii</i> pneumonia (PCP), toxoplasmosis, tuberculosis, <i>Mycobacterium avium</i> complex (MAC), cytomegalovirus (CMV)/herpes simplex virus (HSV)/or varicella zoster virus (VZV), invasive fungal disease, <i>Penicillium marneffe</i> , cryptococcal meningitis, mortality								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment	
What are the effects of primary prophylaxis for <i>Pneumocystis jirovecii</i> pneumonia (PCP) and toxoplasmosis?										
7 (at least 605) [3] [4]	PCP	Trimethoprim–sulfamethoxazole or pentamidine aerosol v placebo for primary prophylaxis against PCP	4	–1	0	–1	0	Low	Quality point deducted for weak methods (incomplete reporting of results, blinding). Directness point deducted for small number of events in 1 RCT (no cases of PCP)	
7 (at least 543) [3] [4]	Mortality	Trimethoprim–sulfamethoxazole or pentamidine aerosol v placebo for primary prophylaxis against PCP	4	–2	0	0	0	Low	Quality points deducted for weak methods (incomplete reporting of results, blinding) and no intention-to-treat analysis in 1 RCT	
14 (unclear) [3]	PCP	Trimethoprim–sulfamethoxazole v pentamidine aerosol for primary prophylaxis against PCP	4	–1	0	–1	0	Low	Quality point deducted for weak methods (incomplete reporting of results, blinding). Directness point deducted for inclusion of data on secondary prophylaxis	
14 (unclear) [3]	Mortality	Trimethoprim–sulfamethoxazole v pentamidine aerosol for primary prophylaxis against PCP	4	–1	0	–1	0	Low	Quality point deducted for weak methods (incomplete reporting of results, blinding). Directness point deducted for inclusion of data on secondary prophylaxis	
13 (unclear) [3] [6]	PCP	Trimethoprim–sulfamethoxazole v dapsone (with or without pyrimethamine) for primary prophylaxis against PCP	4	–1	0	–2	0	Very low	Quality point deducted for weak methods (incomplete reporting of results, blinding). Directness points deducted for inclusion of data on secondary prophylaxis and variable intervention (with or without pyrimethamine)	
13 (unclear) [3] [6]	Mortality	Trimethoprim–sulfamethoxazole v dapsone (with or without pyrimethamine) for primary prophylaxis against PCP	4	–1	0	–2	0	Very low	Quality point deducted for weak methods (incomplete reporting of results, blinding). Directness points deducted for inclusion of data on secondary prophylaxis and variable intervention (with or without pyrimethamine)	
At least 2 (at least 2625) [3] [7]	PCP	High-dose dose trimethoprim–sulfamethoxazole v low-dose trimethoprim–sulfamethoxazole for primary prophylaxis against PCP	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and open-label RCT. Directness point deducted for no direct statistical analysis between groups in one review	
1 (2625) [7]	Mortality	High-dose trimethoprim–sulfamethoxazole v low-dose trimethoprim–sulfamethoxazole for primary prophylaxis against PCP	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and open-label RCT. Directness point deducted for small number of comparators	
1 (545) [3]	Toxoplasmosis	Trimethoprim–sulfamethoxazole v placebo for primary prophylaxis against toxoplasmosis	4	0	0	–2	0	Low	Directness points deducted for small number of events (7 events in total) and for restricted population	
1 (545) [3]	Mortality	Trimethoprim–sulfamethoxazole v placebo for primary prophylaxis against toxoplasmosis	4	0	0	–2	0	Low	Directness points deducted for restricted population and no intention to treat analysis	
8 (unclear) [6]	Toxoplasmosis	Trimethoprim–sulfamethoxazole v dapsone (with or without pyrimethamine) for primary prophylaxis against toxoplasmosis	4	–1	0	–1	0	Low	Quality point deducted for weak methods (incomplete reporting of results, blinding). Directness point deducted for inclusion of data on secondary prophylaxis	

Important outcomes: <i>Pneumocystis jirovecii</i> pneumonia (PCP), toxoplasmosis, tuberculosis, <i>Mycobacterium avium</i> complex (MAC), cytomegalovirus (CMV)/herpes simplex virus (HSV)/or varicella zoster virus (VZV), invasive fungal disease, <i>Penicillium marneffei</i> , cryptococcal meningitis, mortality									
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
8 (unclear) [6]	Mortality	Trimethoprim–sulfamethoxazole v dapsone (with or without pyrimethamine) for primary prophylaxis against toxoplasmosis	4	–1	0	–1	0	Low	Quality point deducted for weak methods (incomplete reporting of results, blinding). Directness point deducted for inclusion of data on secondary prophylaxis
1 (2625) [7]	Toxoplasmosis	High-dose trimethoprim–sulfamethoxazole v low-dose trimethoprim–sulfamethoxazole for primary prophylaxis against toxoplasmosis	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and open-label RCT. Directness point deducted for small number of dose comparators
1 (2625) [7]	Mortality	High-dose trimethoprim–sulfamethoxazole v low-dose trimethoprim–sulfamethoxazole for primary prophylaxis against toxoplasmosis	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and open-label RCT. Directness point deducted for small number of dose comparators
1 (549) [12]	PCP	Atovaquone v pentamidine aerosol for primary prophylaxis against PCP	4	–1	0	–2	0	Very low	Quality point deducted for open-label RCT. Directness points deducted for restricted population (people intolerant of trimethoprim–sulfamethoxazole) and for inclusion of data on secondary prophylaxis
1 (1057) [13]	PCP	Atovaquone v dapsone for primary prophylaxis against PCP	4	–1	0	–1	0	Low	Quality point deducted for open-label RCT. Directness points deducted for restricted population (people intolerant of trimethoprim–sulfamethoxazole)
1 (1057) [13]	Mortality	Atovaquone v dapsone for primary prophylaxis against PCP	4	–1	0	–1	0	Low	Quality point deducted for open-label RCT. Directness points deducted for restricted population (people intolerant of trimethoprim–sulfamethoxazole)
What are the effects of primary antituberculosis prophylaxis in people with HIV infection?									
At least 13 (at least 5595) [14] [15] [16]	Tuberculosis	Antituberculosis regimens v placebo for primary prophylaxis against TB	4	–1	0	0	0	Moderate	Quality point deducted for weak methods in some RCTs (blinding, placebo group received active treatment in 1 RCT, 1 RCT terminated early)
6 (at least 5298) [14] [15] [16]	Mortality	Antituberculosis regimens v placebo for primary prophylaxis against TB	4	–1	–1	0	0	Low	Quality point deducted for weak methods in some RCTs (blinding, placebo group received active treatment in 1 RCT, 1 RCT terminated early, 1 RCT no intention-to-treat analysis). Consistency point deducted for inconsistent effects between population groups (adults, children)
10 (5584) [14]	Tuberculosis	Antituberculosis regimens v each other for primary prophylaxis against TB	4	–1	0	–1	0	Low	Quality point deducted for weak methods (unclear rates of adherence, definitions varying between RCTs). Directness point deducted for different rates of adherence between regimens affecting interpretation of results
11 (5520) [14]	Mortality	Antituberculosis regimens v each other for primary prophylaxis against TB	4	–1	0	–1	0	Low	Quality point deducted for weak methods (unclear rates of adherence, definitions varying between RCTs). Directness point deducted for different rates of adherence between regimens affecting interpretation of results

Important outcomes: <i>Pneumocystis jirovecii</i> pneumonia (PCP), toxoplasmosis, tuberculosis, <i>Mycobacterium avium</i> complex (MAC), cytomegalovirus (CMV)/herpes simplex virus (HSV)/or varicella zoster virus (VZV), invasive fungal disease, <i>Penicillium marneffei</i> , cryptococcal meningitis, mortality									
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
8 (5584) ^[14]	Adverse effects	Antituberculosis regimens v each other for primary prophylaxis against TB	4	-1	0	-1	0	Low	Quality point deducted for weak methods (unclear rates of adherence, definitions varying between RCTs). Directness point deducted for different rates of adherence between regimens affecting interpretation of results
What are the effects of primary prophylaxis for disseminated <i>Mycobacterium avium</i> complex (MAC) disease for people without previous MAC disease?									
1 (174) ^[20]	MAC	Azithromycin v placebo for primary prophylaxis against MAC	4	-1	0	-1	0	Low	Quality point deducted for sparse data. Directness point deducted for restricted population
1 (174) ^[20]	Mortality	Azithromycin v placebo for primary prophylaxis against MAC	4	-2	0	-1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for restricted population
1 (667) ^[23]	MAC	Clarithromycin v placebo for primary prophylaxis against MAC	4	0	0	-1	+1	High	Directness point deducted for restricted population (advanced AIDS). Effect-size point added for HR less than 0.5
1 (667) ^[23]	Mortality	Clarithromycin v placebo for primary prophylaxis against MAC	4	0	0	-1	0	Moderate	Directness point deducted for restricted population (advanced AIDS)
1 (1178) ^[24]	MAC	Clarithromycin plus rifabutin v clarithromycin alone or v rifabutin alone primary prophylaxis against MAC	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (1178) ^[24]	Mortality	Clarithromycin plus rifabutin v clarithromycin alone or v rifabutin alone primary prophylaxis against MAC	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (1178) ^[24]	Adverse effects	Clarithromycin plus rifabutin v clarithromycin alone or v rifabutin alone primary prophylaxis against MAC	4	-1	0	-1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct statistical analysis between individual groups for overall adverse effects or uveitis
1 (693) ^[21]	MAC	Azithromycin plus rifabutin v azithromycin alone or v rifabutin alone for primary prophylaxis against MAC	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (693) ^[21]	Mortality	Azithromycin plus rifabutin v azithromycin alone or v rifabutin alone for primary prophylaxis against MAC	4	-1	0	0	0	Moderate	Quality point deducted for no direct statistical analysis between groups
1 (unclear) ^[21]	Adverse effects	Azithromycin plus rifabutin v azithromycin alone or v rifabutin alone primary prophylaxis against MAC	4	-2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for unclear outcome
What are the effects of secondary prophylaxis for disseminated <i>Mycobacterium avium</i> complex (MAC) disease for people with previous MAC disease?									
1 (160) ^[26]	MAC	Clarithromycin plus ethambutol v clarithromycin plus ethambutol plus rifabutin for secondary prophylaxis against MAC	4	-3	0	0	0	Very low	Quality points deducted for sparse data, open-label RCT, and incomplete reporting of results

Important outcomes: <i>Pneumocystis jirovecii</i> pneumonia (PCP), toxoplasmosis, tuberculosis, <i>Mycobacterium avium</i> complex (MAC), cytomegalovirus (CMV)/herpes simplex virus (HSV)/or varicella zoster virus (VZV), invasive fungal disease, <i>Penicillium marneffei</i> , cryptococcal meningitis, mortality									
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (160) [26]	Mortality	Clarithromycin plus ethambutol v clarithromycin plus ethambutol plus rifabutin for secondary prophylaxis against MAC	4	-3	0	0	0	Very low	Quality points deducted for sparse data, open-label RCT, and incomplete reporting of results
What are the effects of secondary prophylaxis for cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella zoster virus (VZV)?									
1 (unclear) [29]	Herpes simplex virus (HSV), varicella zoster virus (VZV)	Aciclovir v valaciclovir for secondary prophylaxis against HSV or VZV	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (293) [30]	Herpes simplex virus (HSV), varicella zoster virus (VZV)	Valaciclovir v placebo for secondary prophylaxis against CMV, HSV, VZV	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (unclear) [29]	Herpes simplex virus (HSV), varicella zoster virus (VZV)	Different valaciclovir dosage schedules v each other for secondary prophylaxis against CMV, HSV, VZV	4	-1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (48) [31]	Herpes simplex virus (HSV), varicella zoster virus (VZV)	Famciclovir v placebo for secondary prophylaxis against CMV, HSV, VZV	4	-3	0	-2	0	Very low	Quality points deducted for sparse data, high withdrawal rate, and analysis by number of days with symptoms rather than by randomised groups. Directness point deducted for surrogate non-clinical outcome and inclusion of people with recurrent HSV
What are the effects of primary prophylaxis for invasive fungal disease in people without previous fungal disease?									
1 (90) [32]	Invasive fungal disease	Fluconazole v placebo for primary prophylaxis against invasive fungal disease	4	-1	0	-2	0	Very low	Quality point deducted for sparse data. Directness points deducted for small number of events (10 in total) and restricted population
1 (90) [32]	Mortality	Fluconazole v placebo for primary prophylaxis against invasive fungal disease	4	-1	0	-2	0	Very low	Quality point deducted for sparse data. Directness points deducted for small number of events (10 in total) and restricted population
3 (808) [32]	Invasive fungal disease	Itraconazole v placebo for primary prophylaxis against invasive fungal disease	4	0	0	0	+2	High	Effect-size points added for RR less than 0.2
3 (808) [32]	Mortality	Itraconazole v placebo for primary prophylaxis against invasive fungal disease	4	0	0	0	0	High	
1 (636) [33]	Invasive fungal disease	High-dose fluconazole v low-dose fluconazole for primary prophylaxis against invasive fungal disease	4	-1	0	-1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for small number of comparators
1 (636) [33]	Mortality	High-dose fluconazole v low-dose fluconazole for primary prophylaxis against invasive fungal disease	4	-1	0	-1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for small number of comparators
1 (428) [34]	Invasive fungal disease	Fluconazole v clotrimazole troches for primary prophylaxis against invasive fungal disease	4	-1	0	-1	0	Low	Quality point deducted for open-label RCT. Directness point deducted for restricted population

Important outcomes: <i>Pneumocystis jirovecii</i> pneumonia (PCP), toxoplasmosis, tuberculosis, <i>Mycobacterium avium</i> complex (MAC), cytomegalovirus (CMV)/herpes simplex virus (HSV)/or varicella zoster virus (VZV), invasive fungal disease, <i>Penicillium marneffei</i> , cryptococcal meningitis, mortality									
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (428) ^[34]	Mortality	Fluconazole v clotrimazole troches for primary prophylaxis against invasive fungal disease	4	-1	0	-1	0	Low	Quality point deducted for open-label RCT. Directness point deducted for restricted population
What are the effects of secondary prophylaxis for invasive fungal disease in people with previous invasive fungal disease?									
1 (71) ^[40]	<i>Penicillium marneffei</i>	Itraconazole v placebo for secondary prophylaxis against invasive fungal disease	4	-1	0	0	0	Moderate	Quality point deducted for sparse data
1 (71) ^[40]	Mortality	Itraconazole v placebo for secondary prophylaxis against invasive fungal disease	4	-1	0	0	0	Moderate	Quality point deducted for sparse data
1 (108) ^[41]	Cryptococcal meningitis	Itraconazole v fluconazole for secondary prophylaxis against invasive fungal disease	4	-1	0	-1	+2	High	Quality point deducted for sparse data. Effect-size points added for RR less than 0.2. Directness point deducted for small number of events
1 (108) ^[41]	Mortality	Itraconazole v fluconazole for secondary prophylaxis against invasive fungal disease	4	-1	0	-1	0	Low	Quality point deducted for sparse data. Directness point deducted for small number of events
What are the effects of discontinuing primary prophylaxis against opportunistic pathogens in people on highly active antiretroviral treatment (HAART)?									
1 (474) ^[43]	<i>Pneumocystis jirovecii</i> pneumonia (PCP)	Discontinuation v continuation of primary prophylaxis for PCP	4	-1	0	0	0	Moderate	Quality point deducted for open-label RCT
2 (at least 381) ^{[44] [45]}	Toxoplasmosis	Discontinuation v continuation of primary prophylaxis for toxoplasmosis	4	-2	0	0	0	Low	Quality points deducted for open-label RCT and for incomplete reporting of results
2 (1163) ^{[47] [48]}	<i>Mycobacterium avium</i> complex (MAC)	Discontinuation v continuation of primary prophylaxis for MAC	4	0	0	-1	0	Moderate	Directness point deducted for small number of comparators (azithromycin only)
What are the effects of discontinuing secondary prophylaxis against opportunistic pathogens in people on highly active antiretroviral treatment (HAART)?									
2 (259) ^{[43] [49]}	<i>Pneumocystis jirovecii</i> pneumonia (PCP)	Discontinuation v continuation of secondary prophylaxis for PCP	4	-1	0	0	0	Moderate	Quality point deducted for open-label RCTs
1 (57) ^[46]	Toxoplasmosis	Discontinuation v continuation of secondary prophylaxis for toxoplasmosis	4	-2	0	0	0	Low	Quality points deducted for sparse data and open-label RCT
1 (42) ^[66]	Invasive fungal disease	Discontinuation v continuation of secondary prophylaxis for invasive fungal disease	4	-2	0	-1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for small number of comparators (cryptococcus only)

Type of evidence: 4 = RCT Consistency: similarity of results across studies
 Directness: generalisability of population or outcomes
 Effect size: based on relative risk or odds ratio