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REVIEW ARTICLE



Anti-cytomegalovirus preemptive therapy to prevent cytomegalovirus disease in HIV-infected patients: a systematic review

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ABSTRACT

Background: HIV patients are at higher risk of contracting and developing into an asymptomatic form of CMV infection. This review aimed to evaluate the efficacy and safety of preemptive therapy for preventing CMV disease in HIV patients.

Methods: The electronic search was conducted in MEDLINE/PubMed and CENTRAL from inception until 9 September 2022. Studies were included if they assessed the efficacy or safety of anti-CMV preemptive therapy compared to placebo or no therapy. Risk of bias were assessed using the Cochrane Risk of Bias tool for randomized trials version 2 or the Cochrane Collaboration Risk of Bias in Non-randomized Studies of Interventions. The random-effects model was used to calculate effect sizes.

Results: We identified six RCTs (2135 participants) and four observational studies (395 participants), with five RCTs were performed before highly active antiretroviral therapy (HAART) era. Preemptive therapy did not reduce the incidence of CMV disease (RR 0.84, 95% CI: 0.59–1.18), yet reduced the RR of all-cause mortality rate by 26% (RR 0.85, 95% CI: 0.74–0.97) with a low quality of evidence. The incidence of neutropenia as an adverse event increased significantly (RR 2.47, 95% CI: 1.12–5.45) with moderate quality of evidence.

Conclusions: With the advent of HAART, a limited number of studies have been performed to explore anti-CMV preemptive therapy due to the improved outcomes of HIV patients with CMV viremia. Therefore, optimal HAART should take precedence over anti-CMV preemptive therapy. The protocol for this review was registered in the Prospective Register of Systematic Reviews (CRD42020145765).



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Introduction

Opportunistic infections in people with acquired immune deficiency syndrome (AIDS) due to infection of the human immunodeficiency virus (HIV) are important causes of morbidity and mortality. Administration of highly active antiretroviral therapy (HAART) for the first time in 1995 could reduce the incidence of opportunistic infections by 55% from 1992 to 1997 [1], however, preventive strategies remain crucial. Prophylactic regimen includes administration of anti-CMV therapy to immunosuppressed patients who are at risk of CMV infection. Meanwhile, preemptive regimen involves administration of anti-CMV therapy to the patient with evidence of asymptomatic CMV infection detected by CMV assay. A CD4⁺ cell count of <200 cells/ μ L is a condition under which prophylaxis can be considered. In the HAART period, HIV-infected patients with low CD4⁺ cell count and the presence of cytomegalovirus (CMV) dissemination in peripheral blood (detection of plasma CMV DNA and high pp65 antigenemia) are at risk of developing CMV disease [2].

There is lack of recommendation on preemptive strategy in asymptomatic HIV-infected patients due to: (1) limited randomized controlled trials (RCTs) to provide scientific evidence, (2) the high cost of anti-CMV therapy and (3) the possible toxicity [3]. This study is the first systematic review aimed to examine the efficacy and safety of an anti-CMV preemptive regimen in a population of patients with HIV infection. The results of this study can be considered for clinical decision-making in managing opportunistic infections in patients with HIV infection to reveal the best time to provide anti-CMV therapy in conditions of HIV infection.

Methods

Literature search and selection criteria

We searched MEDLINE/PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) database from their inception through 9 September 2022 including publications in any language using HIV, CMV and preemptive-related keywords investigating preemptive therapy in HIV-infected patients with asymptomatic CMV infection (a viremia condition without manifestation of CMV disease) both who had received HAART and were naive. Participants are HIV-infected patients (≥ 13 years of age) suffered from CMV infection without CMV end-organ disease. For intervention, no restrictions on type of antivirals tested for preemptive strategies of CMV

disease. Comparator includes control group. Outcome criteria will be described in the below section. We included a range of study designs, including prospective and retrospective cohort studies, case-control, cross-sectional studies and RCTs. We analyzed controlled trials as cohort, disregarding treatment allocation. We included studies with any number of participants. The complete strategy and search terms are listed in [Supplementary File 1](#). We hand searched the reference lists of all identified studies, relevant review articles and current treatment guidelines for further literature. When we identified more than one publication of an original trial, we assessed these articles together to maximize data collection. We reviewed the data from multiple reports of the same study, so that each study rather than each report was the unit of interest in this review. There were no restrictions on the type, dosage, route of administration or duration of anti-CMV preemptive therapy used. We did not apply any limitation with respect to the length of follow-up. Unique titles and abstracts were then reviewed for eligibility using prespecified Population, Intervention, Comparator, Outcome and Study design criteria.

Outcome measures

The primary endpoint for this study was the efficacy of preemptive therapy in preventing CMV disease, in terms of the incidence of CMV disease during the monitoring period. Secondary outcomes include all-cause mortality and adverse events to assess the safety of the therapy. CMV infection is defined as evidence of CMV replication regardless of symptoms, diagnosed with viral growth *in vitro*, the discovery of viral infection with intranuclear or intracytoplasmic inclusions based on histopathological examination techniques for CMV or findings of replication by testing based on nucleic acid or pp65 antigenemia [4]. CMV syndrome is defined as symptomatic viremia with no end-organ involvement. We defined CMV organ disease as evidence of CMV infection with clinical symptoms or histologic involvement of an organ. Tissue-invasive diseases may include retinitis, central nervous system diseases, gastrointestinal disorders, pneumonitis, hepatitis, nephritis and other manifestations [4]. All-cause mortality was the death recorded during the follow-up study period associated with any cause. CMV therapy adverse events are defined as any untoward medical occurrence that arise after the use of anti-CMV therapy as listed in the references [5] and based on the

Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [6].

Study selection, data extraction and quality assessment

Two review authors independently screened both titles and abstracts of each reference and identified studies that met the eligibility criteria. If unable to reach a consensus, they consulted a third review author to reach a final decision. We documented the study selection process in a flow chart, as recommended in the Preferred Reporting Items for Systematic Reviews (PRISMA) statement [7]. Two review authors independently extracted all data using standardized data extraction forms and assessed eligible studies for methodological quality and risk of bias. The discrepancies between the two review authors were resolved by discussion. In case of any missing or incomplete data, the authors of the trial were contacted for clarification. We extracted the following information: general information, participant characteristics, preemptive treatment, control, outcome, study characteristics and quality assessment. Two review authors independently assess the risk of bias using the Cochrane Risk of Bias 2.0 (RoB2) tool [8] to assess bias of RCTs and the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool to assess bias of cohort studies [9].

Statistical analysis

We performed statistical analysis using the Review Manager 5.4 software. The random-effects model was used to calculate effect sizes. Dichotomous outcomes were analyzed using the risk ratio (RR) measure with 95% confidence intervals (CIs) and presented using forest plots which summarized treatment effect on CMV disease, all-cause mortality and adverse effects. Intention-to-treat analysis was performed if applicable. The statistical heterogeneity among studies was assessed by a χ^2 test on $N-1$ degrees of freedom with an alpha of 0.05 for statistical significance and the I^2 analysis to detect the magnitude of variation attributable to heterogeneity rather than to chance. I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

We pooled data by using the Mantel-Haenzel random-effects model. We also did post hoc sensitivity analyses that excluded data from certain studies. An analysis excluding specific studies was performed to

determine whether these studies could influence the results of the meta-analysis. Subgroup analyses were determined after data extraction.

We rated the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [10]. The protocol for this systematic review was registered in the Prospective Register of Systematic Reviews (PROSPERO) with registry number CRD42020145765 prior to initiation of the review.

Results

Search results

Literature searches of MEDLINE/PubMed, CENTRAL and from manual searching identified 1414 publications according to predefined search criteria. A total of 1364 articles were excluded as irrelevant. A full-text assessment of 50 potentially eligible articles identified 10 eligible studies (10 articles; 2530 participants) [11–20]. Anti-CMV preemptive therapy included 1520 subjects in the treatment groups and 1010 subjects in control groups. The reasons for exclusion of 40 literatures are described in Figure 1. Table 1 outlines the detailed characteristics of the 10 studies included in this systematic review. A list of excluded articles and reasons for exclusion are shown in Supplementary File 2.

The risk of bias of included studies

We rated the overall risk of bias at review level of six RCTs to be of some concerns for four studies and to be high for two studies according to RoB2. We rated four observational studies to have a serious risk of overall bias using the ROBINS-I. Nevertheless, all four studies had a low risk of bias for domains of participant selection, deviation from intervention and outcome measure. The details of the risk of bias assessments will be discussed in the section below for all outcomes.

Data extraction of anti-CMV preemptive therapy in HIV-infected patients

This review identified 6 RCTs with a total of 2135 participants and 4 observational trials with a total of 395 participants. Of the six RCTs, four were conducted in the United States, while two were conducted in Europe. Two observational trials were conducted in Europe, one in Asia and one in Africa. Tests and thresholds for identifying CMV infection varied across the studies, including

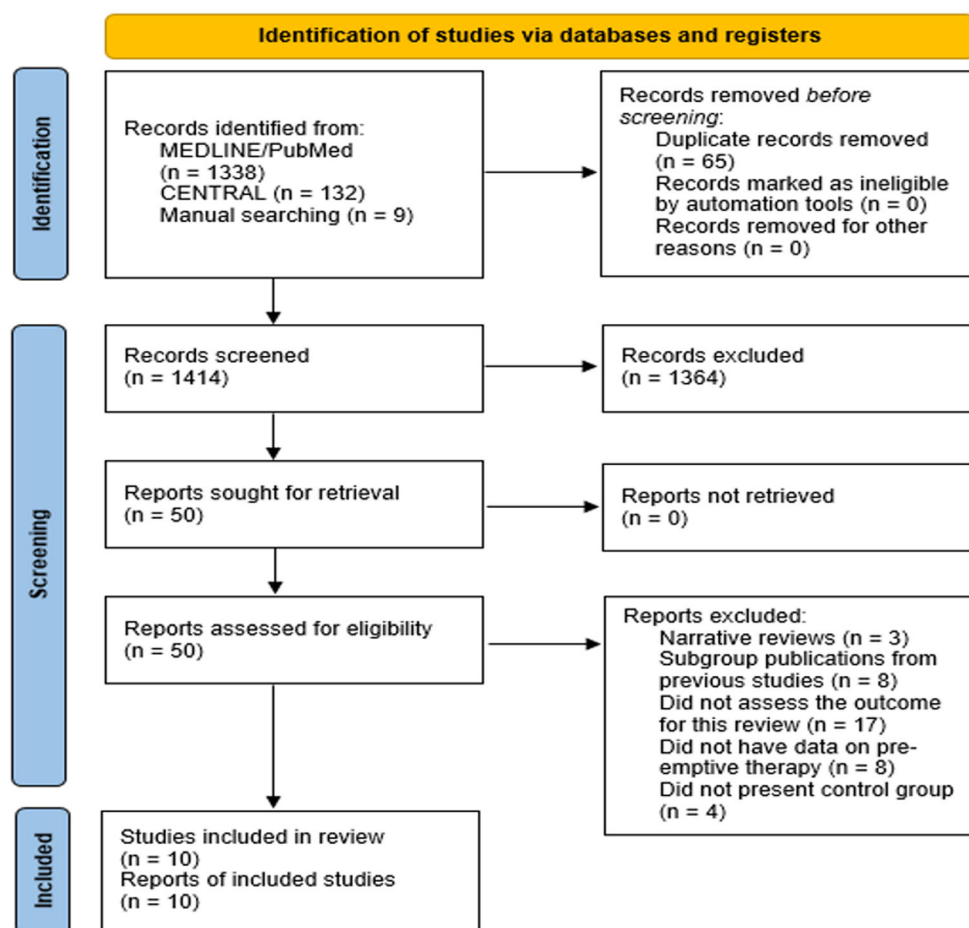


Figure 1. Flowchart of literature selection in this systematic review.

CMV serologic testing, CMV blood culture, CMV urine culture or CMV DNA levels. Follow-up duration of all studies ranged from 19 to 730 days. CIs were wide across most outcomes, indicating considerable imprecision.

A total of 2135 patients were randomized in six RCTs to reveal the effect of preemptive therapy versus placebo or no therapy. Of these patients, follow-up data were not available on 10 patients from the intervention group [11,18] and 5 patients from the control group [18]. The incidence of CMV disease (16.1% versus 20.7%) and death (28.3% versus 34.3%) were found to be lower in the preemptive therapy group compared to placebo or no therapy. Among the 15 reported adverse event outcomes from these RCTs, 2 outcomes with a significant incidence in the intervention group were neutropenia (18.2% versus 12%) and increased creatinine level (20.1% versus 12.8%).

Outcome analysis of four included observational studies revealed the incidence of CMV disease to be lower in the intervention group (15.2%) than in the control one

(22.5%). However, all-cause mortality from observational studies was higher in the preemptive therapy arm (16.2% versus 13.7%). The incidence of neutropenia in the preemptive therapy was significantly increased in the preemptive therapy group by 20.9% in these observational studies.

Analysis of anti-CMV preemptive therapy versus control

This section discusses four outcomes of preemptive therapy which include two efficacy and two adverse event outcomes from both RCTs and observational trials.

CMV disease

Eight of 10 included studies reported the outcome of developing CMV disease. Event rate of this outcome in the preemptive therapy group ranged from 10% to 60% and ranged from 7.27% to 80.95% in the control group. No significant difference was found between the preemptive therapy group and the control group for CMV

Table 1. Summary of characteristics of the included studies.

Study	Design	Setting	N	Characteristics of participants	Intervention	Outcomes	Follow-up (median, days)
Balfour et al. 1996 [11]	RCT	Multicenter study The United States, May 1992–August 1993	27 (no follow up data: 2)	HIV-infected patients, age ≥ 18 years (median 37 years), CD4+ < 200 cells/mm ³ , positive CMV blood cultures (four weeks before inclusion), no CMV disease, all received ART but 18.5% stopped (median four months)	Foscarnet 15 mg/kgBW every 8 h Foscarnet 30 mg/kgBW every 8 h Foscarnet 45 mg/kgBW every 12 h Foscarnet 90 mg/kgBW every 12 h intravenously for 10 days Ganciclovir 3 g per day per oral	CMV and HIV-1 viremia rates Death CMV disease CMV survival Toxicity	398
Brosigart et al. 1998 [13]	RCT	Multicenter, double-blind study The United States, April 1993–June 1994	994	HIV-infected patients, age ≥ 13 years (median: intervention group 39.5 years, control group 39.4 years), CD4+ ≤ 100 cells/mm ³ (median: intervention group 35 cells/mm ³ , control group 33 cells/mm ³), positive CMV serology or positive CMV blood culture, without CMV disease, 75.5% of the intervention group and 74.1% of control group received ART		Safety and efficacy of ganciclovir CMV disease CMV survival Toxicity	Intervention 453, placebo 447
Salmon-Ceron et al. 1999 [17]	RCT	Multicenter study, phase 2, open-label trial France, February 1993–December 1995	42	HIV-infected patients, age > 18 years, CD4+ < 100 cells/mm ³ (median: intervention group 9 cells/mm ³ , control group 10 cells/mm ³), two CMV positive blood cultures (within three months before inclusion), without CMV disease, no data on ART	Foscarnet 100 mg/kgBW every 12 h intravenously for 14 days	Elimination of viremia on day 14 Time to CMV viremia relapse CMV disease Adverse effects	Intervention 237, control 318
Spector et al. 1996 [18]	RCT	Multicenter, double-blind study The United States, November 1992–December 1993	725 (drop out: intervention 8, control 5)	HIV-infected patients, median age of the intervention group 39 years, control group 38 years, CD4+ < 50 cells/mm ³ or < 100 cells/mm ³ with opportunistic infections (mean: intervention group 26 ± 19.6 cells/mm ³ , control group 27 ± 19.7 cells/mm ³), CMV antibody test positive or CMV urine culture positive, without CMV disease, 94% received ART	Ganciclovir 1000 mg three times daily orally	Safety and efficacy of ganciclovir CMV disease	367
Wohl et al. 2009 [19]	RCT	Multicenter, double-blind study The United States, August 2000–April 2004	47	HIV-infected patients, median age 46 years, CD4+ < 100 cells/mm ³ (median 12 cells/mm ³), CMV seropositive, no CMV disease, 78.7% receiving ART	Valganciclovir 900 mg twice daily orally for three weeks	Time to develop CMV disease (a combination of probable and confirmed) CMV disease Death	383
Youle et al. 1994 [20]	RCT	Multicenter, double-blind study The United Kingdom, November 1989–December 1991	202	HIV-infected patients, median age of the intervention group 38 years, control group 39 years, CD4+ ≤ 150 cells/mm ³ (median: intervention group 36 cells/mm ³ , control group 41 cells/mm ³), CMV seropositive, no CMV disease, 98% of the intervention group and 97% of control group received ART	Acyclovir 800 mg four times daily orally for 48 weeks	Time to develop CMV and other herpesvirus disease Survival	365
Bigliano et al. 2018 [12]	Cohort study	Single-center study Italy (no data on period)	157	HIV-infected patients, median age 48.3 years, CD4+ < 350 cells/mm ³ (median: intervention group 39 cells/mm ³ , control group 74 cells/mm ³), subgroup CMV viremia, no CMV disease, 100% receiving ART	Ganciclovir 5 mg/kgBW twice daily intravenously for two weeks followed by once daily for two weeks	Five-year survival	No information
Mattioni et al. 2015 [14]	Cohort study	Single-center study France, 1 January 2007 – 31 December 2007	71	HIV-infected patients, median age of intervention group 44 years, control group 43 years, median CD4+ intervention group 26 cells/mm ³ , control group 80 cells/mm ³ , CMV viremia, no CMV disease, 50% of the intervention group and 55% of control group receiving ART	Valganciclovir ($n = 12$), ganciclovir ($n = 1$), ganciclovir followed by valganciclovir ($n = 1$), foscarnet ($n = 1$) or a combination of ganciclovir, valganciclovir, foscarnet and cidofovir ($n = 1$)	CMV disease Death Adverse events	420

(continued)

Table 1. Continued.

Study	Design	Setting	N	Characteristics of participants	Intervention	Outcomes	Follow-up (median, days)
Mayaphi et al. 2014 [15]	Cohort study	Single-center study, ICU setting South Africa, 2009–2012	41	HIV-infected patients, median age 37 years, CD4+ <200 cells/mm ³ , median 29 cells/mm ³ , detectable CMV viral load, no CMV disease, 78% did not receive ART	Ganciclovir 5 mg/kgBW twice daily intravenously for 21 days	CMV viral load kinetics Death	19
Mizushima et al. 2013 [16]	Cohort study	Single-center study Japan, 1 January 2000 – 31 December 2006	126	HIV-infected patients, age >17 years (median: intervention 44 years, control 41 years), CD4+ <100 cells/mm ³ (intervention median 28 cells/mm ³ , control 35.5 cells/mm ³), positive plasma CMV DNA, no CMV disease, all had never received ART	Induction: ganciclovir 5 mg/kgBW every 12 h intravenously, valganciclovir 900 mg every 12 h orally or foscarnet 90 mg/kg every 12 h intravenously Maintenance: ganciclovir 5 mg/kgBW every 24 h intravenously, valganciclovir 900 mg every 24 h orally or foscarnet 90 mg/kgBW every 24 h intravenously given for a minimum of seven days	CMV disease	730

disease outcome (Figure 2, with eight studies, 2332 participants: RR 0.84, 95% CI: 0.59–1.18) with significant heterogeneity $I^2 = 63\%$, $p = .008$. Sensitivity analysis was conducted by excluding studies that did not fulfill the current clinical setting (studies before the HAART period as well as studies with withdrawn drugs) and excluding studies with a high risk of bias showed high heterogeneity (80% and 56% respectively) with a relative similar risk for CMV disease. Subgroup analyses based on the types of studies included were consistent with the results that preemptive therapy was not shown to reduce the incidence of CMV disease.

The only RCT after the advent of HAART failed to detect a significant difference in terms of reduction in CMV disease occurrence following preemptive therapy. CMV end-organ disease was diagnosed in 4 of 24 participants from the preemptive arm and 6 of 23 participants from the placebo arm. This study might be underpowered due to the small sample size obtained, which was 47 of the previously calculated 60 subjects to achieve 80% power. This study was halted as it was very unlikely to achieve the primary objective due to the limited number of patients eligible for enrollment into randomization and the unexpectedly low rate of CMV end-organ disease in the placebo group [19].

We rated the overall risk of bias at outcome level for CMV disease to be high in two RCTs [11,19] and two observational studies [14,16]. Study by Balfour was considered to have high risk of bias because it did not report CMV disease outcomes in 2 of 27 participants [11]. Study by Wohl presented high risk of bias because the reported outcomes included probable CMV disease [19]. From the aspect of the intervention given, two observational studies had serious risk of bias because the types of preemptive therapy given to their participants were various [14,16].

All-cause mortality

Preemptive therapy group reported all-cause mortality rate of 6.9% to 76.19% and control group reported rate of 5.2% to 76.19%. Preemptive therapy reduced the risk for all-cause mortality (10 studies, 2530 participants: RR 0.85, 95% CI: 0.74–0.97), no significant heterogeneity was found among the studies ($I^2 = 7\%$, $p = .37$), as displayed in Figure 3. The results of the sensitivity analysis excluding studies with a high risk of bias showed consistent results that the intervention could reduce all-cause mortality. When analyses were performed by excluding studies conducted before HAART and excluding studies with withdrawn drugs, there was no

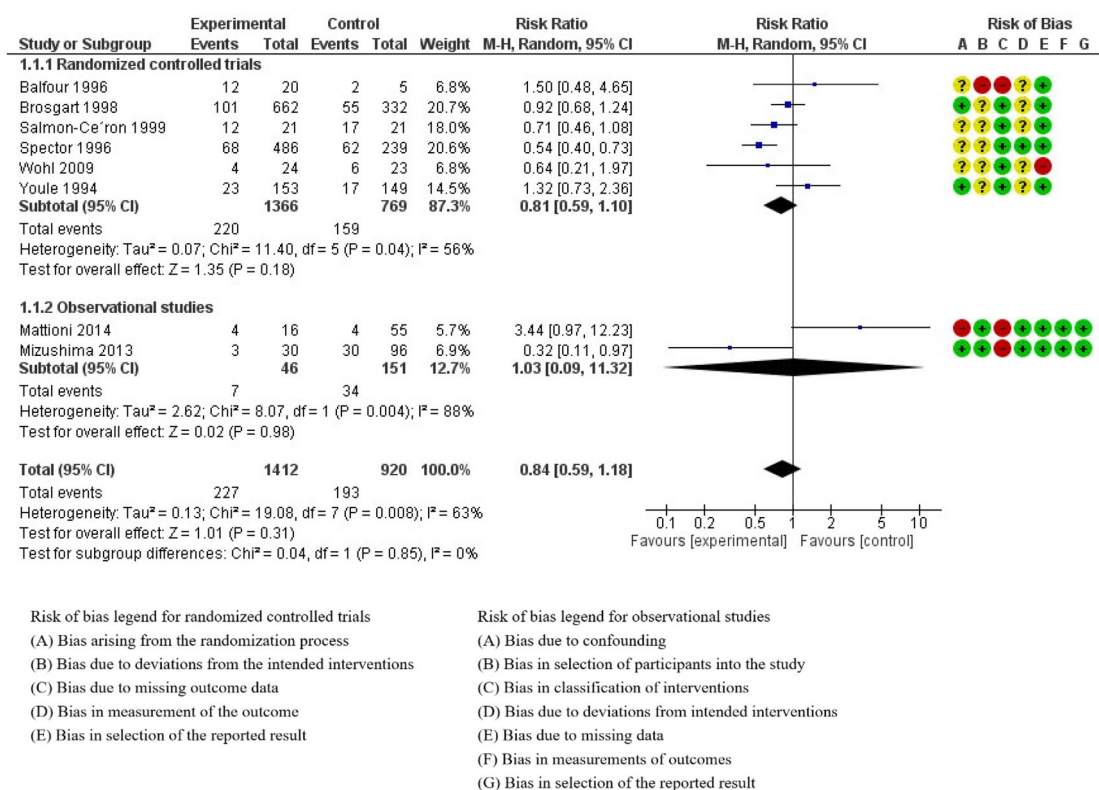


Figure 2. Anti-CMV preemptive therapy versus control: CMV disease.

significant difference in the incidence of all-cause mortality between the two groups. RCT in the HAART era by Wohl reported mortality outcomes in 7 of 24 participants in the preemptive therapy and 8 of 23 participants in the control group. The causes of death were considered not directly associated with CMV infections [19]. Subgroup analysis also showed that data from observational studies contributed to the absence of a protective effect of preemptive therapy on all-cause mortality in HIV-infected patients with a heterogeneity of 45%.

We rated the overall risk of bias at outcome level for all-cause death to be high in one RCT and all observational studies. Study by Balfour was considered to have high risk of bias as it did not report CMV disease outcomes in 2 of 27 participants [11]. We judged the risk of bias due to confounding factors to be serious for three studies because participants in the intervention group had lower baseline CD4+ cell counts and higher levels of CMV DNA than controls, which could affect the outcome of mortality in the intervention group [12,14,15]. From the aspect of the intervention given, three studies had serious risk of bias because the types of preemptive therapy given were various in two studies [14,16] and one study included patients with delayed therapy [15].

Neutropenia

A total of five studies reported the occurrence of neutropenia [13–16,18]. preemptive therapy and control group reporting neutropenia had a mean rate of 18.39% (range, 12.5–25.94%) and 9.23% (range, 11.46–12.82%), respectively. Compared to those of controls, the incidence of neutropenia increased in the preemptive therapy group (Figure 4, with five studies, 1944 participants: RR 2.47, 95% CI: 1.12–5.45) with high heterogeneity ($I^2 = 74\%$, $p = .004$). A sensitivity analysis excluding studies with a high risk of bias resulted in a consistently increased outcome of neutropenic adverse event. Exclusion of studies that did not match the current clinical setting (studies before the HAART period and studies with withdrawn drugs) resulted in a data analysis similar to that of a subgroup analysis of three observational studies reporting the incidence of neutropenia, in which the increased risk of neutropenia was 20.23 with very wide 95% CI (3.83–106.82). Subgroup analysis of RCTs showed that administration of preemptive therapy did not result in an increased risk of neutropenic adverse event in the intervention group.

We rated the overall risk of bias at outcome level for neutropenia to be high in all three observational studies. We judged the risk of bias in selection of the reported

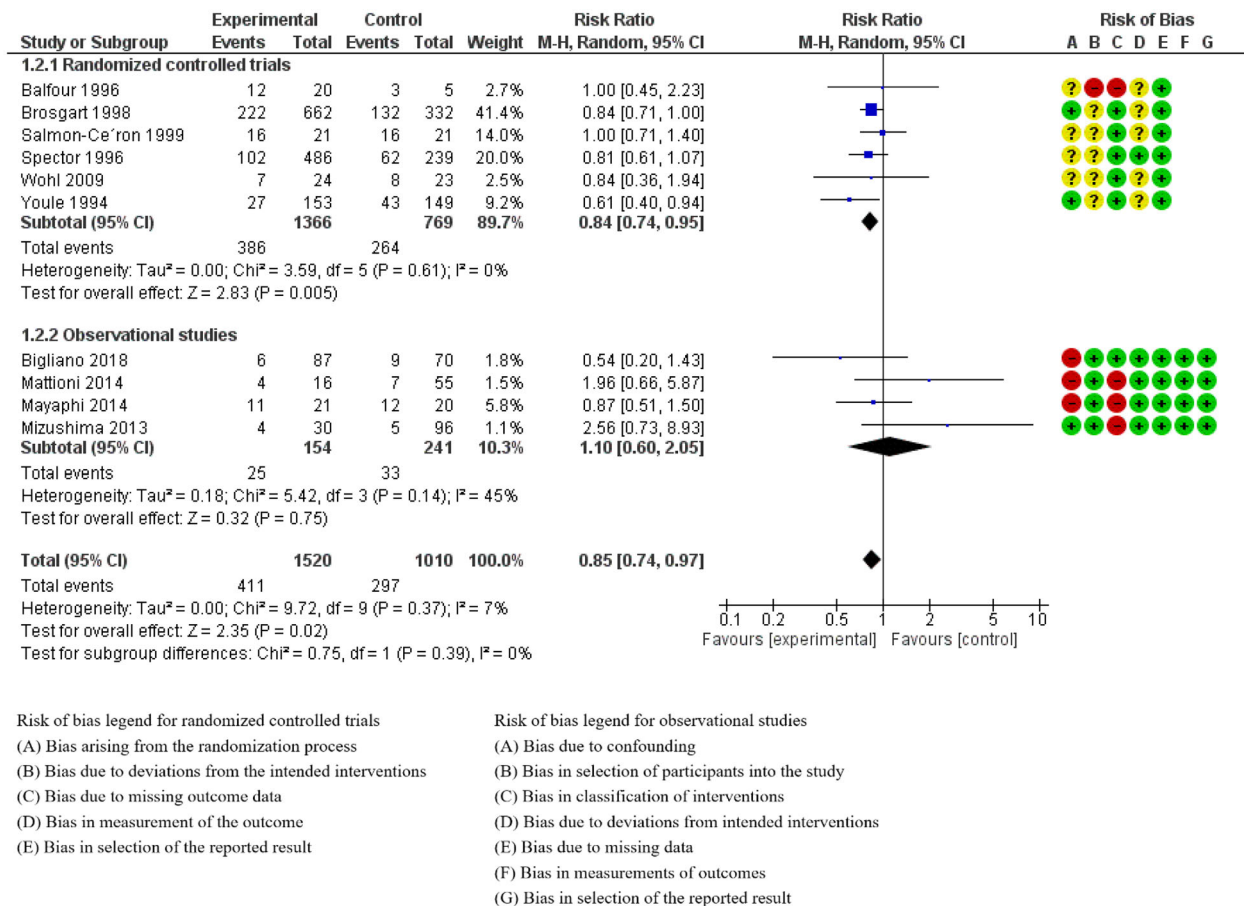


Figure 3. Anti-CMV preemptive therapy versus control: all-cause death.

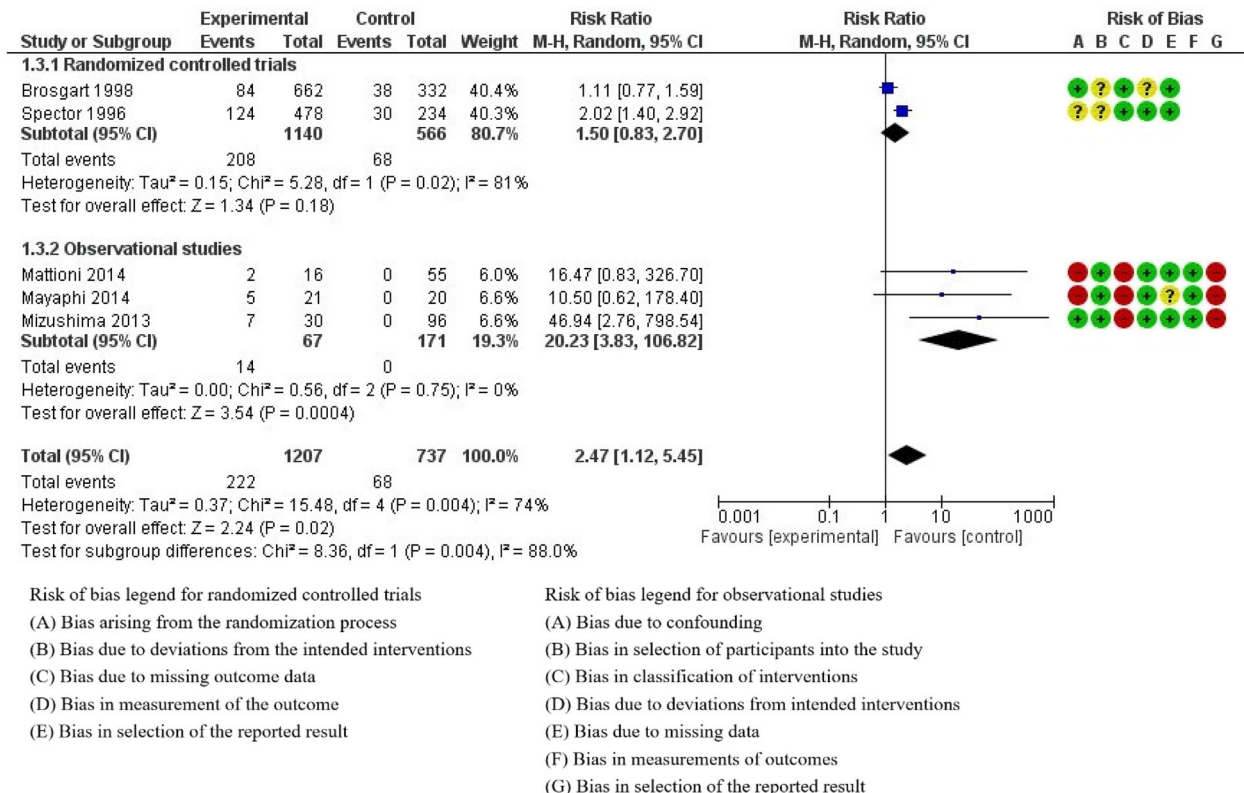


Figure 4. Anti-CMV preemptive therapy versus control: neutropenia.

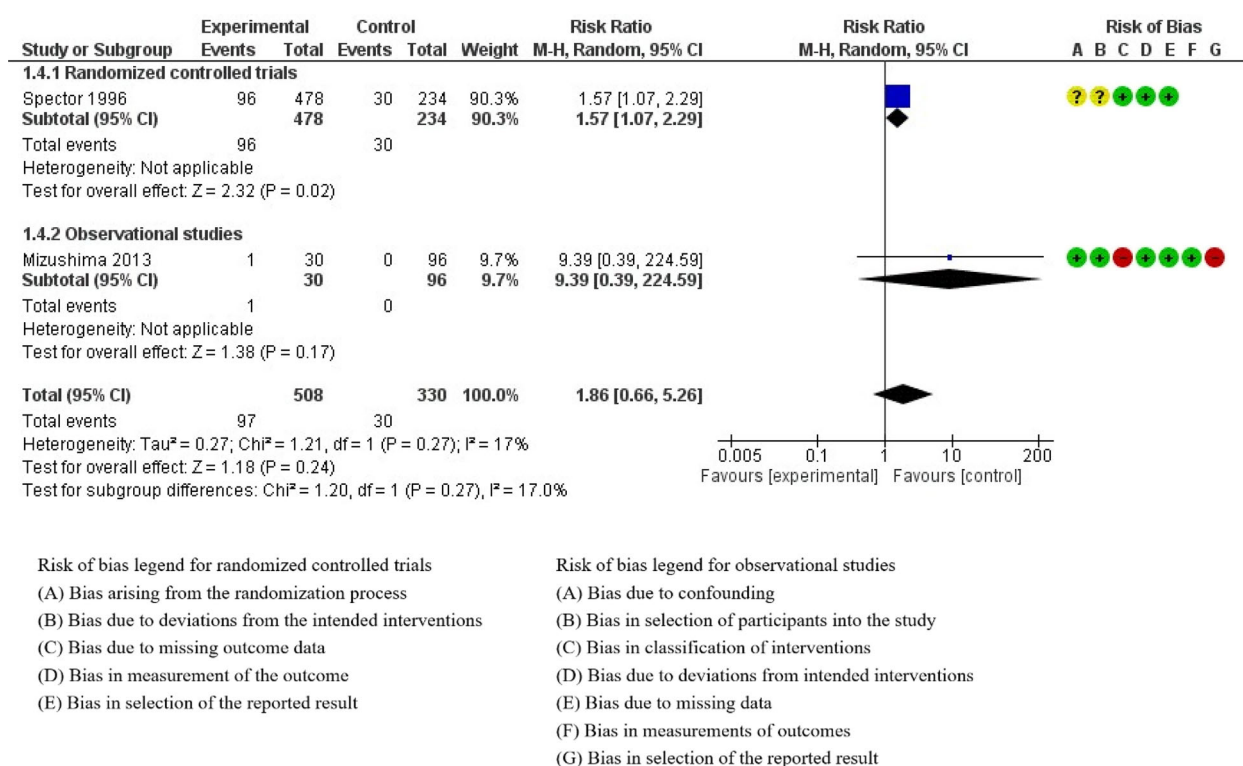


Figure 5. Anti-CMV preemptive therapy versus control: increased creatinine level.

results to be critical in three studies because they reported adverse event for the intervention group only [14–16].

Increased creatinine level

The relative risk of preemptive therapy strategies for increased creatinine level was 1.86 with no significant difference compared to control group (two studies, 838 participants: RR 1.86, CI: 95% 0.66–5.26) with heterogeneity $I^2 = 17\%$, $p = .27$ (Figure 5). RCT reported preemptive therapy yielded an increased creatinine rate of 20.1% and control group of 12.8%. In contrast, the observational studies tended to report increased creatinine level only in the preemptive therapy group without providing data from control group.

We rated the overall risk of bias at outcome level for increased creatinine level to be high in the included observational study. We judged the risk of bias in the selection of the reported results to be critical as the observational study reported various types of preemptive therapies and provided no adverse event data for the control group [14–16].

Overall result

Table 2 shows a summary of findings comparing anti-CMV preemptive therapy versus placebo or no therapy

in all included studies in this systematic review. The administration of preemptive therapy for CMV infection in this study did not show a significant reduction in the risk of CMV disease compared to placebo or no therapy (eight studies, 2332 participants: RR 0.84, 95% CI: 0.59–1.18, $I^2 = 63\%$, $p = .008$). The quality of scientific evidence for these outcomes is low due to bias both in RCTs (incomplete descriptions of randomization, no blinding in some studies, reporting of selective outcomes) and in observational studies (imbalance in baseline between the two groups, varying preemptive therapies given related to observational study design), as well as the heterogeneity of the output data.

The meta-analysis revealed reduction of all-cause mortality in the preemptive therapy compared to control group (10 studies, 2530 participants: RR 0.85, 95% CI: 0.74–0.97, $I^2 = 7\%$, $p = .37$). The quality of evidence for this outcome is moderate because there is bias in both the RCTs and the included observational studies. We could not establish how often infections led to death because the cause of death was not provided in most included studies.

Discussion

HAART as a therapy for HIV was introduced in the period 1995–1996 [21]. The RCTs investigated in this

Table 2. Summary table of findings comparing preemptive anti-CMV versus placebo or no therapy.

Anti-CMV preemptive therapy compared with control for HIV-infected patients

Patients or population: HIV-infected patients

Settings: hospital

Intervention: preemptive therapy (six randomized controlled trials and four observational studies)

Comparison: placebo or no therapy

Outcomes	Illustrative comparative risks ^a (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Preemptive therapy			
CMV disease	Study population 210 per 1000	Study population 162 per 1000 (136 to 193)	RR 0.84 (0.59 to 1.18)	2332 (8 studies)	⊕⊕⊕⊖ Low ^{b,c}
All-cause mortality	Study population 294 per 1000	Study population 244 per 1000 (215 to 276)	RR 0.85 (0.74 to 0.97)	2530 (10 studies)	⊕⊕⊕⊖ Low ^{b,c}
Neutropenia	Study population 92 per 1000	Study population 159 per 1000 (125 to 203)	RR 2.47 (1.12 to 5.45)	1944 (5 studies)	⊕⊕⊕⊕ Moderate ^b
Increased creatinine	Study population 91 per 1000	Study population 146 per 1000 (101 to 213)	RR 1.86 (0.66 to 5.26)	838 (2 studies)	⊕⊕⊕⊖ Low ^{b,d}

Note: CI: confidence interval; RR: risk ratio.

^aThe basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).^bDowngraded for serious risk of bias.^cDowngraded for serious inconsistency.^dDowngraded for serious imprecision.

review were mostly conducted before the HAART period [11,13,17,18,20]. During this period, HIV therapy were single therapy or two combinations of nucleoside analog drugs such as zidovudine, didanosine, zalcitabine or stavudine. When the included studies in this review were conducted, the use of high doses of acyclovir or ganciclovir per oral was still an option of therapy. However, oral ganciclovir is currently out of production and CMV management guidelines do not recommend high-dose acyclovir [22–24].

The results of the sensitivity analysis, excluding studies conducted before the HAART period, and studies with drugs that have been withdrawn from the market show that preemptive therapy did not result in a reduced risk of CMV disease (RR 0.86, CI: 95% 0.22–3.36) and all-cause mortality (RR 1.01, 95% CI: 0.64–1.61). The only one RCT performed in the HAART period had a high risk of bias because it did not provide data that discriminated between probable and confirmed CMV with no information regarding the blinding of outcome assessors. Due to the low incidence of CMV end-organ disease in this trial, the investigators suggest that anti-CMV preemptive therapy may not be warranted in the HAART era. The low 12-month incidence rate (14% among CMV-viremia patients who received HAART, compared to estimated incidence of 38%–50%) led to decrease the statistical power in detecting any significant difference between the study arms [19]. HIV and CMV co-infection conditions have a complex immune

mechanism and are different from single infections [25] so that the provision of anti-CMV preemptive therapy needs to be accompanied by adequate HIV therapy.

With the advent of HAART, the incidence of CMV disease as one of the highly feared viral complications of AIDS has significantly declined [26]. HAART suppresses CMV viremia as it is highly efficient in reducing HIV replication, therefore, increasing CD4+ T cell count [27]. The introduction of HAART alone may control CMV retinitis as this can induce undetectable CMV DNA by PCR without any CMV therapy [26,28]. The incidence of CMV retinitis has dramatically decreased by 75–85% with an improvement in survival by 93% [26,28]. The use of HAART in patients with retinitis CMV resulted in fewer ocular complications and decreased the risk of retinal detachment leading to vision loss [28].

Regressed replication of CMV may be mediated by controlling HIV replication subsequent transactivation in cells co-infected with CMV or increasing circulating TNF-alpha. Immunological control of CMV replication in HAART recipients is associated with the production of CMV-specific interferon-gamma as seen from *in vivo* experiments following simulation by peripheral blood mononuclear cells. These immunological changes could be the mechanism underlying the suppression of CMV replication following HAART administration [26].

The incidence of neutropenia in this systematic review was found to be significantly higher in the preemptive therapy arm with moderate quality of scientific

evidence, while the risk for elevated creatinine cannot be inferred from the results of the included studies (Supplementary File 3). Since the reporting of adverse events can be biased in open-label studies, some studies should be judged carefully in terms of reported drug-related toxicity [11,17]. Meta-analyses yielded wide CIs, making it difficult to measure the true efficacy of these interventions.

No consensus regarding anti-CMV preemptive therapy for people with HIV exists while the issues of efficacy, safety and economics remain. Published studies have not been able to provide evidence regarding the advantages or disadvantages of preemptive therapy in this population, considering that most RCTs were carried out in the period before HAART and some of the therapies used in these studies are no longer applied for anti-CMV therapy. Oral ganciclovir and oral acyclovir used during the study period were no longer the therapeutic options for CMV infection. The current types of antiviral recommended for anti-CMV therapy are oral valganciclovir, intravenous ganciclovir, intravenous foscarnet and intravenous cidofovir [22–24].

There were different tests used to define CMV infection in the studies included in this review, for instance, CMV serologic testing, CMV blood culture, CMV urine culture and CMV DNA levels. This variability between studies may decrease the confidence to draw definite conclusions about the application of preemptive therapy in HIV-infected patients with CMV infection. The low cut-off value in diagnosing CMV infection leads to earlier detection of infection and allows early initiation of therapy to prevent CMV disease. On the other hand, high cut-offs can delay therapy and potentially increase the incidence of preventable CMV disease.

Less is known in terms of the optimal timing for HAART initiation relative to the commencement of anti-CMV treatment in HAART-naïve patients with newly diagnosed CMV retinitis [29]. It is worth noting that immune recovery vitritis or uveitis can occur in HAART recipients as a consequence of the altered immune response. The eye is the main target of this CMV-associated immune recovery syndrome that occurs in patients previously-diagnosed with CMV retinitis due to the sudden increase in the number of CD4+ cells on HAART [26].

As the risk of patients with HIV developing opportunistic infection drops significantly in the HAART period. Therefore, rather than focusing on preemptive therapy, we would encourage to make sure the optimal administration of HAART. However, routine ophthalmic

monitoring is indicated since CMV retinitis still occurs in patients who fail to respond to HAART [27] and progression may continue even in patients who responded well to HAART [28].

This systematic review does have some limitations and the quality of evidence obtained from data analysis are not strong enough to influence clinical decision-making regarding the use of anti-CMV preemptive therapy in the HAART period. This is due to the improved outcome of HIV-infected patients with CMV viremia following HAART administration and the limited number of RCTs with good methodologies for assessing the provision of anti-CMV preemptive therapy in a population with HIV. Additionally, most of the included RCTs were performed in the period before HAART which did not represent current conditions. The data from observational trials also cannot provide conclusive quality of evidence due to differences in the baseline of the two groups and the different types of anti-CMV preemptive therapy administered. The individual efficacy of anti-CMV drug could not be separately evaluated due to insufficient data.

Conclusions

Preemptive therapy did not reduce the incidence of CMV disease, but it could slightly reduce all-cause mortality rate with a low quality of evidence. The incidence of neutropenia adverse events increased significantly with moderate quality of evidence. The quality of evidence from the studies included in this systematic review was insufficient to recommend the administration of anti-CMV preemptive therapy in HIV-infected patients. Furthermore, improved outcomes of HIV-infected patients with CMV viremia have been observed with the advent of HAART. Therefore, optimal HAART should take precedence over anti-CMV preemptive therapy. Provision of HAART therapy as early as possible needs to be considered in people with HIV/AIDS to prevent opportunistic infections.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its [supplementary materials](#).

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