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Review

Antiviral prophylaxis in haematological patients: Systematic review and meta-analysis

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ABSTRACT

Purpose: Antiviral prophylaxis is commonly prescribed to haematological cancer patients. We conducted a systematic review and meta-analysis to quantify its overall benefit in specific clinical scenarios.

Methods: Randomised controlled trials assessing antiviral prophylaxis versus placebo, no treatment, pre-emptive treatment or another antiviral drug were included. Patients undergoing haematopoietic stem cell transplantation (HSCT) or intensive chemotherapy for acute leukaemia or high-grade lymphoma were included. No restrictions on language, year or publication status were applied. Overall mortality, herpes simplex virus (HSV) and cytomegalovirus (CMV) diseases were assessed as primary outcomes. Pooled relative risks (RRs) and numbers needed to treat (NNT) with 95% confidence intervals (CI) are reported.

Results: HSCT was the condition assessed in 22 trials and intensive chemotherapy in 5 trials. In the pre-engraftment setting of autologous or allogeneic HSCT, antiviral prophylaxis (mainly acyclovir for HSV seropositive recipients) significantly reduced HSV (NNT 2, 2–2, control event rate (CER) 61.9%) and CMV disease, with no effect on overall mortality. In the allogeneic post-engraftment setting (mainly CMV-seropositive recipients/donors), antiviral prophylaxis resulted in a significant reduction in overall mortality, RR 0.79 (0.65–0.95), NNT 12 (7–50, CER 39.4%) and all viral-related outcomes. In this setting, acyclovir significantly reduced overall mortality (RR 0.71, 0.53–0.96, 4 trials) and ganciclovir/maribavir significantly reduced CMV disease (RR 0.26, 0.14–0.48, 5 trials). During chemotherapy, acyclovir significantly decreased HSV disease (NNT 3, 2–4, CER 37.4%) and infection rates, with no effect on mortality.

Conclusions: Antiviral prophylaxis reduced mortality with a small NNT in the post-engraftment setting of allogeneic HSCT. In the pre-engraftment phase and during chemotherapy only viral-related morbidity was reduced.

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1. Introduction

Herpesviruses are a major cause of morbidity and mortality among haematological patients undergoing haematopoietic stem-cell transplantation (HSCT) or receiving myelosuppressive chemotherapy.[1–3] Following allogeneic transplantation the risk for herpes simplex virus (HSV) infection is approximately 80%, for cytomegalovirus (CMV) is 20–30% and for varicella zoster virus (VZV) is 20–50%, among seropositive recipients without prophylaxis.[4]

Current guidelines recommend antiviral prophylaxis for allogeneic HSCT recipients, against HSV pre-engraftment and against CMV or VZV post-engraftment, tailored to recipients' serostatus for each virus.[4–8] Prophylaxis against other viruses is recommended on an individual basis. The drawback of these guidelines is that they address individual viruses and by their respective serologies. However, in clinical practice we treat an individual patient with a single antiviral drug and our aim is to improve the overall morbidity and mortality. Most adults are seropositive to more than one herpesvirus; in the United States (US), seroprevalences are 58.9% for CMV, 57.7% for HSV type 1 and above 99% for VZV.[9–11]

Our systematic review aims to quantify the overall gain afforded by antiviral prophylaxis for the individual patient in specific clinical scenarios.

2. Methods

2.1. Inclusion criteria and outcomes

We included randomised controlled trials that assessed adults or children following haematopoietic stem cell transplantation or following intensive chemotherapy for acute leukaemia or high-grade lymphoma. We included trials that compared any antiviral agent and placebo, no treatment, a preemptive strategy or another antiviral agent. Pre-emption was included together with placebo/no treatment in the comparison of antiviral prophylaxis and no prophylaxis. Trials comparing different doses, schedule and methods of administration of the same antiviral drug were excluded, as were studies in which all patients had proof of active viral infection at baseline.

The primary outcomes assessed were overall mortality at the end of follow-up, HSV disease and CMV disease. The secondary outcomes included CMV pneumonitis, HSV and CMV infections, VZV disease, rebound HSV, CMV and VZV infections or diseases after drug discontinuation, adverse events requiring discontinuation of study drugs, neutropaenia attributed to study drugs and other serious adverse events. Herpesvirus 'disease' was defined as documentation of the virus in conjunction with tissue invasive disease (including mucocutaneous disease) or fever with no alternative cause for, while 'infection' was defined as the finding of positive culture, antigenaemia or PCR (polymerase chain reaction) tests with or without clinical manifestations. We intended to extract the data on all-cause mucositis and pneumonitis, bacterial and fungal infections, length of hospitalisation, time to viral infection/disease and emergence of drug resistance, but these outcomes were rarely reported and could not be compiled. The analyses were separated by the clinical scenario: HSCT pre-engraftment; HSCT post-engraftment; and intensive chemotherapy (without HSCT). The trials that commenced antiviral prophylaxis pre-engraftment and continued the intervention beyond 30 d after transplantation were included both in the pre-engraftment and in the post-engraftment analyses (conducted separately).

2.2. Search strategy and selection criteria

We searched the Cochrane Register of Controlled Trials (CENTRAL), PubMed and LILACS databases. Unpublished trials were sought in the references of all selected studies, relevant conference proceedings, trial registries, ongoing trial databases, new drug application documents and personal contacts with the investigators of included trials. No language, publication or date restrictions were imposed. The search strategy is displayed in Fig. 1; the last search was performed in November 2008.

2.3. Study selection and data extraction

Two reviewers independently performed the search, applied inclusion criteria and extracted the data. Outcomes were extracted preferably by intention to treat (ITT) and, if missing, by as-treated. The missing data were requested from the authors.

Risk of bias was assessed and its effect on outcomes was assessed through sensitivity analyses. Allocation concealment and generation were graded as adequate, unclear or inadequate, using criteria suggested in the Cochrane handbook.[12]

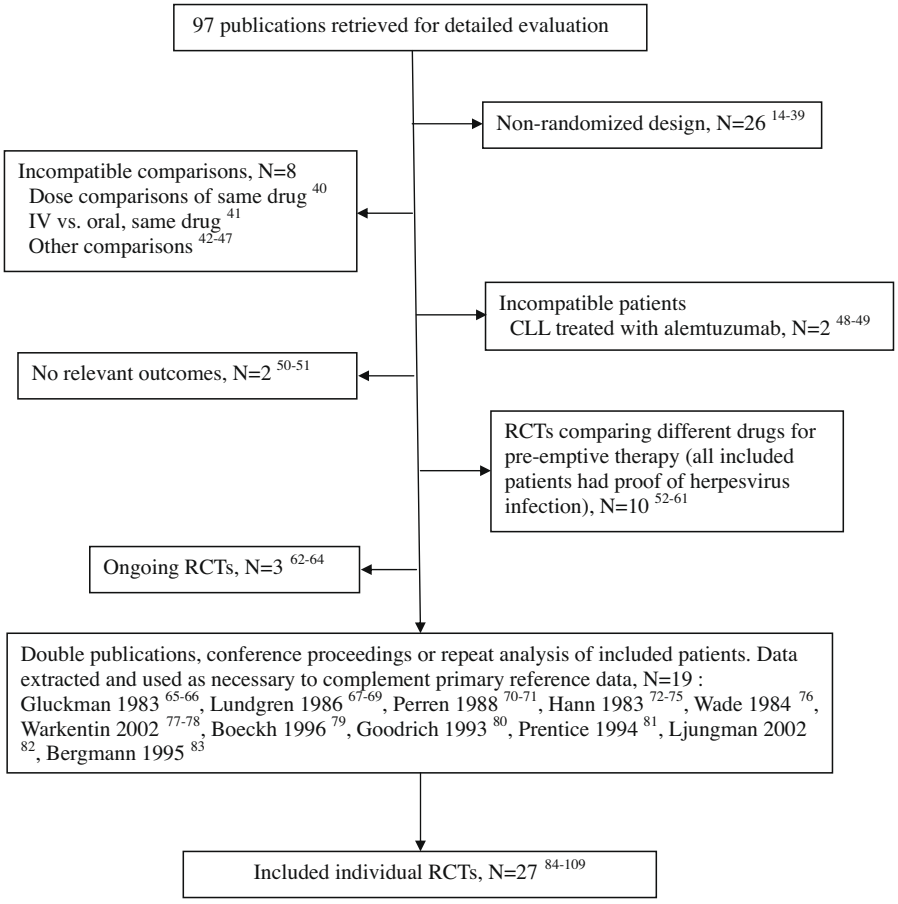
2.4. Statistical analysis

Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for individual trials. Meta-analysis was performed using the Mantel–Haenszel-fixed effects model. The numbers needed to treat or harm (NNT or NNH) were calculated as 1/risk-difference obtained by meta-analysis of individual study risk differences. Heterogeneity in the results of the trials was assessed using the chi-square test for heterogeneity and the I^2 measure of inconsistency.[13] Heterogeneity was defined using the inconsistency statistic as $I^2 > 50\%$.[12] The random effects model was used when significant heterogeneity was detected. We investigated heterogeneity through subgroup analyses by type of antiviral drug and the use of placebo, no treatment or pre-emptive strategy for control.

A funnel plot was visually inspected for the primary outcomes to assess small study's effect. Analysis was conducted using RevMan 5.0.

3. Results

The search yielded 224 potentially relevant publications, of which 127 were irrelevant and 97 were further evaluated. Fifty one trials were excluded[14–64] and 19 were double publications[65–83] (Fig. 1). Twenty seven randomised controlled trials were included in the review (Table 1).[84–109]



Search strategy: The terms prophylaxis, prevention and preemptive were combined with the term antiviral and with specific drugs and viruses names. All of these were also combined with the medical subject heading terms hematological diseases, hematological neoplasms, bone marrow transplantation or stem cell transplantation and with the Cochrane filter for randomized controlled trials in PubMed [12]

Fig. 1 – Search strategy and trial flow.

Twenty two trials assessed patients undergoing HSCT, mostly allogeneic. The interventions were assessed as pre-engraftment in 7 trials, post-engraftment in 11 trials and during both phases in 4 trials (Table 1). Five trials assessed the patients who were given intensive chemotherapy, mainly for acute leukaemia. The definitions used in the individual studies for viral-related outcomes are given in Table A1.

Risk of bias in included trials is reported in Table 1. Of the 22 HSCT trials, adequate allocation concealment was described in five trials and 17 were double blind. All five chemotherapy trials were double blinded and adequate allocation concealment was reported in one.

3.1. *HSCT pre-engraftment*

3.1.1. *Antiviral prophylaxis versus placebo (9 trials, 442 patients)*

One trial assessed autologous HSCT,[93] 3 trials included a minority (<20%) of patients undergoing autologous HSCT[84,90,94] and the remaining included patients undergoing allogeneic HSCT. The study drug was acyclovir in all but one trial that assessed ganciclovir.[87] All recipients were HSV seropositive in five trials and the median rate in the other 4 trials was 52% (range 45–66%). CMV seropositivity was reported in 4 trials (median 64%, range 43–100%).

There was no significant difference in the overall mortality for antiviral prophylaxis versus placebo (as treated RR 0.98, 0.68–1.42, 6 trials, 264 patients; and ITT RR 1.05, 0.80–1.37, 6 trials, 310 patients, Fig. 2). HSV disease rates were significantly lower with the intervention (RR 0.19, 0.11–0.31, NNT 2, 2–2, 7 trials, 226 patients, Fig. 3). CMV disease rates were significantly lower with prophylaxis (RR 0.59, 0.37–0.94, NNT 11, 6–100, 6 trials, 300 patients, Fig. 4). There was no significant heterogeneity for the primary outcome comparisons. Sensitivity analyses by risk of bias for mortality did not reveal different results. The funnel plots for mortality and CMV disease were symmetric while HSV disease showed a small study's effect in favour of prophylaxis.

Table 1 – Characteristics of included trials.

Study	Condition assessed	Intervention	Intervention onset	Duration of therapy (max)	Follow up on mortality	N	Age (years)	Study years	Industry sponsor	Location	Baseline sero-positive	End of follow up	Risk of bias[a]
HSCT, pre- and post-engraftment													
Engelhard 1988[84]	Combined allo/auto GVHD grade 2–4: 4% Total body irradiation (TBI): 93% T-cell depletion: 83%	Oral ACV versus placebo	6 d before transplantation	96 d	90 d after transplantation	29	2–53	1985–1986	No	Israel	100% HSV (R)	104 d after transplantation	A, A, O
Ljungman 1986[85]	Allogeneic Unmatched donors: 14% GVHD 2–4: 42% TBI: 100%	IV+oral ACV versus placebo	5 d before transplantation	185 d	1 year after transplantation	42	Mean 20.8 ± 2.3 versus 18.3 ± 2.9	1982–1984	Yes	Sweden	74% CMV (R and/or D), 50% HSV (R), 86% HSV (R and/or D)	1 year after transplantation	B, A, DB
Perren 1988[86]	Allogeneic Unmatched: 16% TBI: 100%	IV+oral ACV versus placebo	1 d before transplantation	180 d	No mortality results	82	95% <40	1983–1986	Yes	UK	43% CMV (R), 66% HSV (R), 48% VZV (R)	1 year after transplantation	B, B, DB
Winston 1993[87]	Allogeneic Unmatched: 12% GVHD 2–4: 35% TBI: 39% T-cell-depletion: 39%	IV GCV versus placebo	7 d before transplantation	127 d	120 d after transplantation	130	14–50	1987–1990	No	USA	100% CMV (R), 57% CMV (D), 55% HSV (R), 62% VZV (R)	120 d after transplantation	B, B, DB
HSCT, pre-engraftment													
Gluckman 1983[88]	Allogeneic Unmatched: 0% GVHD 2–4: 52% TBI: 100%	Oral ACV versus placebo	8 d before transplantation	43 d	Up to 545 d	40	2–37	1981	Yes	France	53% CMV (R), 45% HSV (R)	100 d after transplantation	B, B, DB
Hann 1983a[89]	Allogeneic TBI: 100%	IV ACV versus placebo	On day of transplantation	Until neutropaenia resolved	End of treatment	20	Mean 23	1983	Yes	UK	100% HSV (R)	10–24 months after transplantation	A, B, DB
Liesveld 2002[93]	Autologous TBI: 0%	IV ACV versus oral Val	On day of transplantation	Mean 12 d (range 9–18 d)	End of treatment	30	Median 50 (26–69)	2002	Yes	USA	100% HSV (R)	30 d after transplantation	A, A, O
Saral 1981[90]	Combined allo/auto	IV ACV versus placebo	3 d before transplantation	18 d	80 d from entry	20	6–51	1980–1981	Yes	USA	100% HSV (R)	80 d after transplantation	A, B, DB
Shepp 1985[91]	Allogeneic	IV ACV versus placebo	6 d before transplantation	22 d	No mortality results	30	16–45	1985	Yes	USA	100% HSV (R)	100 d after transplantation	A, A, DB
Wade 1984[92]	Allogeneic TBI: 100%	Oral ACV versus placebo	7 d before transplantation	35 d	105 d after transplantation	49	9–55	1984	Yes	USA	100% HSV (R)	15 weeks after transplantation	B, B, DB
Warkentin 2002[94]	Combined allo/auto/ chemotherapy	Oral ACV versus oral Val	On day of transplantation or first day after completing chemotherapy	Median 16 d (range 1–90 d)	No mortality results	151	17–76	1998–2000	Yes	Canada	100% HSV (R)	Not given	B, B, OA
HSCT, post-engraftment													
Boeckh 1996[95]	Allogeneic Unmatched: 17% GVHD 2–4: 76% TBI: 74%	IV GCV versus IV GCV preemptive	At engraftment	Median 39 d (range 0–83 d)	400 d after transplantation	231	0.8–60	1992–1994	No	USA	100% CMV (R), 65% CMV (D)	400 d after transplantation	A, B, DB
Boeckh 2006[96]	Allogeneic Unmatched: 16% GVHD 2–4: 36%	Oral ACV versus placebo	>30 d after transplantation	1 year	1 year	84	10–65	2006	No	USA	100% VZV (R)	For mortality 1 year after transplantation, for infection – 5 years	A, B, DB

			onset	of therapy (max)	mortality			years	sponsor		positive		
Boeckh 2008[97]	Allogeneic	Oral VGC versus oral VGC/IV GCV preemptive	>80 d after transplantation	150–190 d	No mortality results	184	>16	2001–2007	No	USA	100% CMV (R and/or D)	640 d after transplantation	B, B, DB
Burns 2002[103]	Allogeneic TBI: 93% T-cell-depletion: 30%	IV GCV versus oral ACV	At engraftment	<100 d (engraftment to day 100 post transplantation)	1 year	91	1.1–55	2002	No	USA	100% CMV (R), 45% CMV (D)	1 year after transplantation	B, B, O
Goodrich 1993[98]	Allogeneic Unmatched: 35% GVHD 2–4: 49% TBI: 71% T-cell-depletion: 0%	IV GCV versus placebo	At engraftment	<100 d (engraftment to day 100 post transplantation)	180 d after transplantation	70	4–57	1990–1991	No	USA	100% CMV (R)	180 d after transplantation	B, B, DB
Ljungman 2002[104]	Allogeneic Unmatched: 7% GVHD 2–4: 17% TBI: 64% T-cell-depletion: 14%	Oral ACV versus oral Val	28 d after transplantation	98 d	154 d after transplantation	748	13–60	2002	Yes	Europe	100% CMV (R and/or D)	22 weeks after transplantation	A, A, DB
Pineiro 1997[99]	Allogeneic	Oral GCV versus placebo	At engraftment	<100 d (engraftment to day 100 post transplant)	No mortality results	27	NR	1997	Yes	USA	100% CMV (R)	100 d after transplantation (end of treatment)	B, B, DB
Prentice 1994[100]	Allogeneic GVHD 2–4: 25% TBI: 65% T-cell-depletion: 19%	Oral ACV versus placebo	30 d after transplantation	180 d	1 year	310	Mean 30.5	1994	Yes	Europe	100% CMV (R and/or D)	1 year after transplantation	B, B, DB
Shepp 1987[101]	Allogeneic	Oral ACV versus placebo	30 days after transplantation	45 d	No mortality results	51		1987	Yes	USA	100% HSV (R), 41% CMV (R)	100 d after transplantation	A, B, DB
Winston 2003[105]	Allogeneic Unmatched: 8% GVHD 2–4: 36% TBI: 50% T-cell-depletion: 5%	IV GCV versus oral Val	At engraftment	Median 68 d (range 1–87 d)	180 d after transplantation	168	13–66	1995–1998	Yes	USA	100% CMV (R), 57% CMV (D)	6 months after transplantation	B, B, O
Winston 2008[102]	Allogeneic GVHD 2–4: 28%	Oral MBV versus placebo	At engraftment	<84 d (engraftment to 12 weeks post transplantation)	End of treatment	111	19–64	2008	Yes	USA	100% CMV (R), 52% CMV (D)	8 weeks after end of treatment	B, B, DB
Chemotherapy													
Anderson 1984[106]	Acute leukaemia or high-grade lymphoma	Oral ACV versus placebo	Onset of chemotherapy	42 d	42 d (end of chemotherapy)	40	17–75	1984	Yes	UK	75% HSV seropositive R	9–10 weeks	B, B, DB
Bergmann 1995[107]	Acute leukaemia	Oral ACV versus placebo	Onset of chemotherapy	28 d	28 d (end of chemotherapy)	90	18–84	1989–1993	Yes	Denmark	100% HSV seropositive R	28 d (end of treatment)	A, B, DB
Hann 1983b[89]	Acute leukaemia	IV ACV versus placebo	Onset of chemotherapy	Until neutropaenia resolution	End of therapy	40	Mean 27	1983	Yes	UK	100% HSV seropositive R	10–24 months	A, B, DB
Lonqvist 1993[108]	Acute leukaemia	Oral ACV versus placebo	Onset of chemotherapy	Mean 86 d (SD 22 d)	End of therapy	116	15–74	1993	Yes	Sweden	87% HSV seropositive R	End of treatment	B, A, DB
Saral 1983[109]	Acute leukaemia	IV ACV versus placebo	Day +4 of chemotherapy onset	32 d or less	End of therapy	30	16–75	1982–1983	Yes	USA	100% HSV seropositive R	6 months after completion of study	A, B, DB

Abbreviations: N – number of patients included in trial. HSCT – haematopoietic stem cell transplantation. Combined allo/auto – study included both patients receiving allogeneic and autologous transplantations. ACV – acyclovir, GCV – ganciclovir, Val – valacyclovir, VGC – valganciclovir, MBV – maribavir, HSV – herpes simplex virus, CMV – cytomegalovirus, VZV – varicella zoster virus, R – recipient and D – donor.

a The first letter is a grade for allocation generation, and the second letter is a grade for allocation concealment; both are graded as A for adequate and B for unclear or unknown methods. The third letter denotes blinding: DB, double-blind; OL, open-label, OA, outcome assessor.

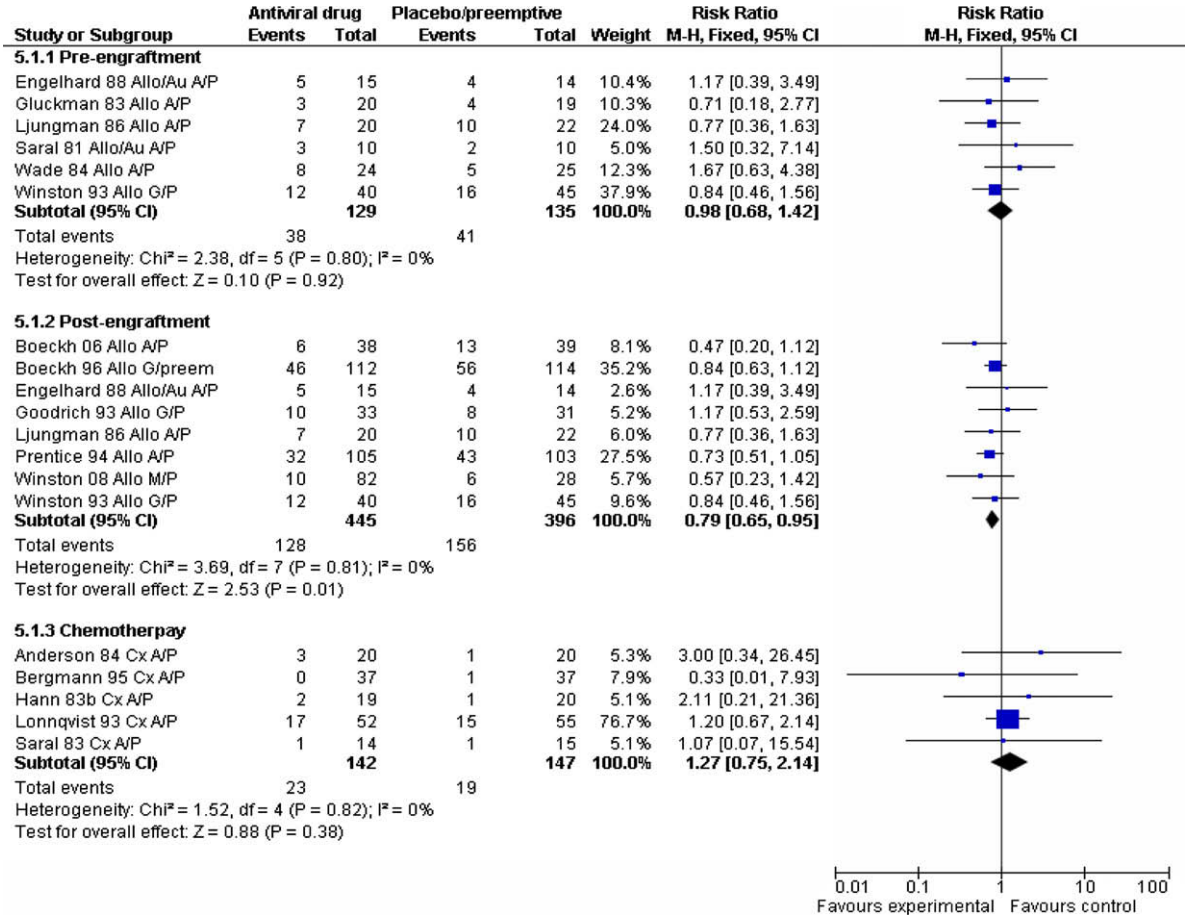


Fig. 2 – Overall mortality for antiviral prophylaxis versus placebo/no treatment or pre-emptive treatment. The forest plot is sub-grouped by the clinical scenario: HSCT pre-engraftment, HSCT post-engraftment and intensive chemotherapy for acute leukaemia or high-grade lymphoma. Study names comprise of the first author and year of publication; the condition assessed (allo – allogeneic HSCT, au – autologous HSCT, Cx – chemotherapy, comb – all three combined); and the interventions assessed (A – acyclovir, G – ganciclovir, Va – valacyclovir, VGC – valganciclovir, M – maribavir, preemp – pre-emptive therapy, P – placebo). RR scale range 0.01–100.

Other viral-related outcomes are given in Table 2. HSV infection rates were lower with prophylaxis. HSV-rebound disease and infection were higher following prophylaxis versus placebo, but the analyses showed heterogeneity and the NNTs to prevent HSV during prophylaxis were lower than the NNH for HSV rebound after prophylaxis discontinuation. Both CMV pneumonitis and overall CMV infection rates were lower with prophylaxis, with a low NNTs and no significant rebound effect. Exclusion of one trial using ganciclovir[87] reduced the effect for all CMV-related outcomes and the results were no longer significant. VZV disease or infection rates were significantly lower with antiviral prophylaxis (Fig. A1). The NNT to prevent VZV during prophylaxis was equal to the NNH with regard to the rebound VZV after prophylaxis cessation, but the benefit during treatment was based on more trials.

Adverse events requiring treatment discontinuation occurred in 3/79 patients treated with acyclovir versus 0/78 without (5 trials), a difference that was not statistically significant. Ganciclovir caused significantly more neutropaenia compared to placebo (RR 1.65, 1.00–2.70) in one trial, but discontinuations were not reported in this trial.[87] Acyclovir-resistant HSV strains were detected in 1/14 patients treated with acyclovir versus 2/13 with placebo in one trial[91], while three trials reported no resistant isolates.[85,89,92]

3.1.2. *Head to head comparisons*

Two trials[93,94] (908 patients) compared acyclovir and valacyclovir (Table 1). No significant differences between these two drugs were found in all review outcomes.

3.2. *HSCT post-engraftment*

3.2.1. *Antiviral prophylaxis versus placebo/pre-emptive therapy (12 trials, 1249 patients)*

Six trials assessed acyclovir,[84–86,96,100,101] 4 trials assessed ganciclovir,[87,95,98,99] one trial assessed valganciclovir[97] and one trial assessed maribavir.[102] In 7 trials all recipients and/or donors were CMV seropositive[87,95,97–100,102] and in the remaining

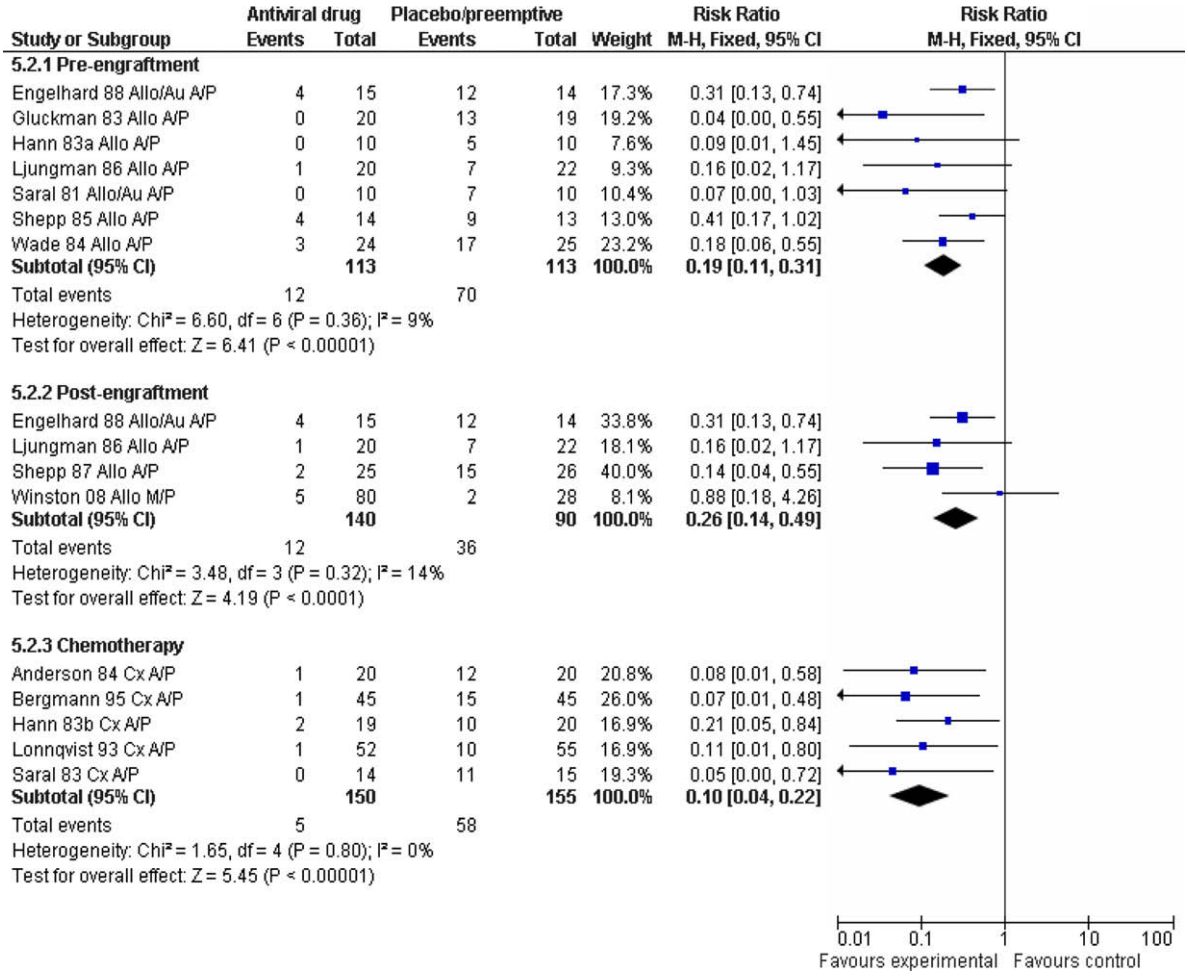


Fig. 3 – HSV disease for antiviral prophylaxis versus placebo/no treatment or pre-emptive treatment. Abbreviations as for Fig. 2. RR scale range 0.002–500.

5 trials the median was 48% (range 41–74%). HSV recipient seropositivity was reported in 5 trials; in 2 trials all patients were HSV seropositive[84,101] and the range in others was 45–86%. The median prophylaxis duration was 100 d post-transplant (range 35–365).

Overall mortality rates were significantly lower in the intervention group (as-treated RR 0.79, 0.65–0.95, 8 trials, 841 patients, NNT 12, 7–50, Fig. 2). A trend towards lower mortality was also demonstrated by intention-to-treat, reported in fewer studies (RR 0.83, 0.66–1.03, 5 trials, 493 patients). Mortality (as-treated) was significantly lower in the studies that assessed acyclovir (RR 0.71, 0.53–0.96, 4 trials, 356 patients) and non-significantly lower with ganciclovir or maribavir (RR 0.84, 0.66–1.07, 4 trials, 485 patients). This trend did not change when excluding the only trial that used pre-emptive therapy as control for ganciclovir.[95] HSV disease rates were significantly reduced with prophylaxis (RR 0.26, 0.14–0.49, NNT 4, 3–6, 4 trials, 230 patients), a difference driven by 3 trials that assessed acyclovir in this comparison (Fig. 3). CMV disease rates were also significantly lower with antiviral prophylaxis (RR 0.42, 0.29–0.62, NNT 12, 9–20, 7 trials, 962 patients, Fig. 4). The differences were significant with ganciclovir/maribavir (RR 0.26, 0.14–0.48, 5 trials) and non-significant with acyclovir (RR 0.69, 0.43–1.13, 2 trials). There was no significant heterogeneity in all primary outcome comparisons. Sensitivity analyses for the trials' methodological quality showed similar results for mortality in trials with adequate allocation generation and double-blinding (adequate allocation concealment was reported in one trial only). The funnel plots for mortality and HSV were symmetric, while CMV disease showed a small study's effect in favour of prophylaxis.

HSV infection rates were reduced to a similar degree as HSV disease rates and the NNH after prophylaxis cessation were twice that needed to treat for both outcomes (Table 2). A benefit was shown in all trials, with heterogeneity stemming from trials assessing antivirals other than acyclovir (RR 0.20, 0.10–0.40 for acyclovir only, $I^2 = 0\%$). Similarly, CMV pneumonitis and infection rates were reduced and the risk for rebound infection or disease was not statistically significant. Heterogeneity in the analysis for CMV infection was due to a lack of benefit with acyclovir (RR 0.90, 0.62–1.28) as compared to other antivirals (RR 0.42, 0.31–0.56). VZV occurred significantly less frequently during prophylaxis (Fig. A1) and significantly more frequently after prophylaxis, but more trials reported on the benefit during prophylaxis than on the harm after cessation.

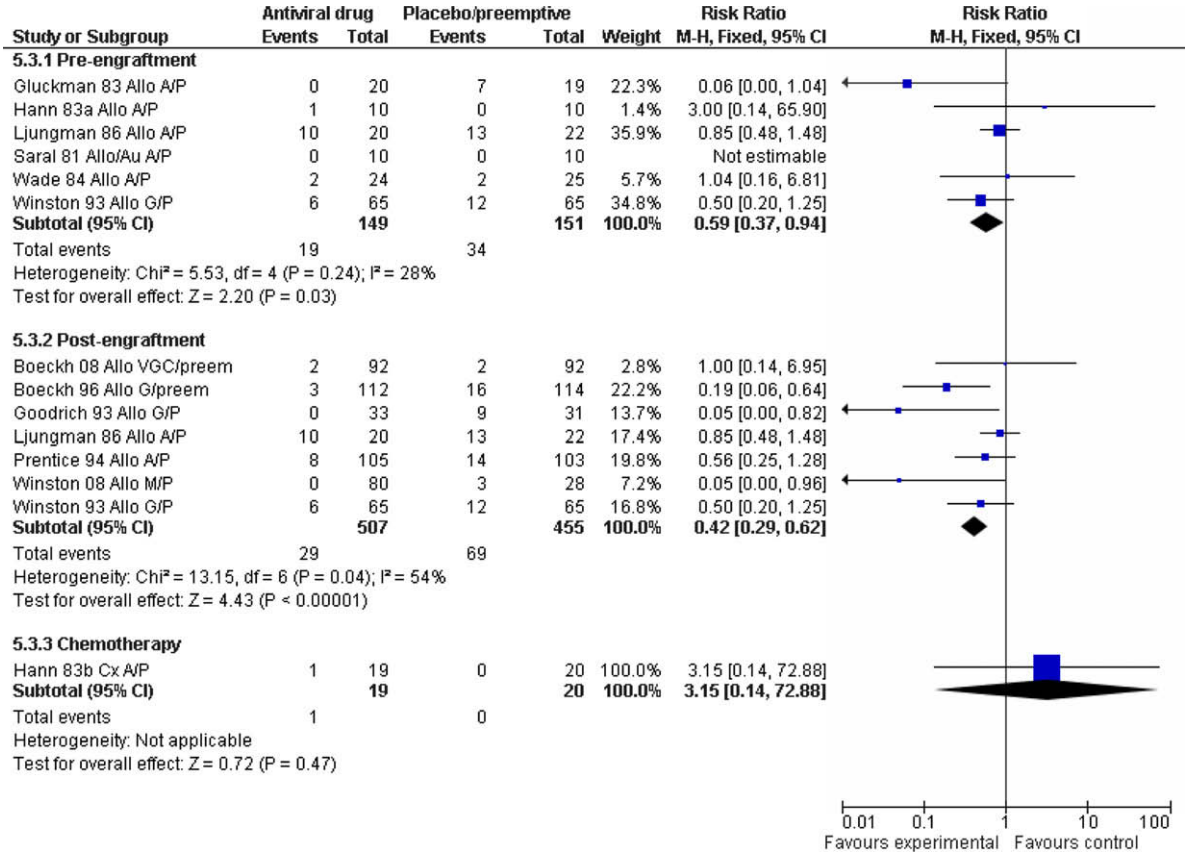


Fig. 4 – CMV disease for antiviral prophylaxis versus placebo/no treatment or pre-emptive treatment. Abbreviations as for Fig. 2. RR scale range 0.002–500.

Discontinuation of study drug due to adverse events was more frequent with ganciclovir (RR 4.34, 1.80–10.44, 3 trials, 420 patients, NNH 9, 6–17) and acyclovir (RR, 4.01, 0.47–34.43, not statistically significant). Neutropaenia was significantly more prevalent with ganciclovir/maribavir compared with placebo/pre-emptive treatment (RR 1.35, 1.07–1.72, 5 trials, 676 patients); with acyclovir the difference was not statistically significant (RR 2.28, 0.35–15.07, 2 trials, 106 patients). Haemolytic uraemic syndrome/thrombotic thrombocytopaenic purpura (HUS/TTP) was reported in one trial in two patients treated with maribavir.[102] Resistance development was reported as null in three trials.[85,102,105]

3.2.2. *Head to head comparisons*

Two trials (259 CMV seropositive patients) compared ganciclovir and acyclovir or valacyclovir. There was no significant difference in efficacy with RRs favouring ganciclovir for mortality (ITT RR 0.78, 0.58–1.04) and CMV disease (RR 0.47, 0.14–1.61). HSV disease was not reported. Adverse events requiring discontinuation of study drug were significantly more common with ganciclovir (RR 7.05, 1.93–25.75). One case of TTP/HUS was reported with valacyclovir versus none with ganciclovir.

One trial compared oral acyclovir and valacyclovir, demonstrating no significant differences with regard to all primary and secondary outcomes, adverse events and TTP/HUS.[104]

3.3. *Antiviral prophylaxis versus placebo for intensive chemotherapy (5 trials, 316 patients)*

The study drug was acyclovir in all trials. Prophylaxis was started with chemotherapy and continued during the neutropaenic phase in all trials for a median of 32 d (range 28–100 d). All recipients were HSV seropositive in 3 trials, and 75% and 87% of patients were HSV seropositive in the other 2 trials. None reported on CMV serostatus.

There was no significant difference in overall mortality between study groups (as treated, RR 1.27, 0.75–2.14, 5 trials, 289 patients; ITT RR 1.10, 0.50–2.40, 2 trials, 130 patients, Fig. 2). HSV disease rates were significantly lower with acyclovir (RR 0.10, 0.04–0.22, NNT 3, 2–4, 5 trials, 305 patients, Fig. 3). There was no significant heterogeneity in these analyses. CMV disease was reported in a single trial reporting one event of pneumonitis with acyclovir.[89] The number of studies was too small for meaningful sensitivity or funnel plot analyses.

HSV infection rates were significantly lower with the intervention, with a NNT of 2 (1–3) and no rebound effect (Table 2). CMV infection rates reported in two trials and VZV reported in a single trial were not significantly different. All-cause oral mucositis rates were reported in a single trial and were significantly lower with acyclovir prophylaxis (RR 0.30, 0.12–0.75).[107] There was no significant difference with regard to adverse events (4 trials). Reduced acyclovir susceptibility was described in one patient treated with acyclovir, with recurrent

Table 2 – Viral-related outcomes.

Outcome	RR [95% CI]	I^2 (%)	N trials	N patients	NNT/NNH (95% CI), ER[a]
Antiviral prophylaxis versus placebo/pre-emptive therapy in the pre-engraftment period of HSCT					
HSV disease	0.19 [0.11, 0.31]	9	7	226	2 (2–2), 61.9%
HSV infection	0.23 [0.11, 0.49]	69	9	393	3 (2–7), 52.5%
Rebound HSV disease	2.33 [1.30, 4.16]	46	7	226	7 (4–17), 9.7%
Rebound HSV infection	3.07 [0.88, 10.75]	57	7	288	NS[b]
CMV disease	0.59 [0.37, 0.94]	28	6	300	11 (6–100), 22.5%
CMV pneumonitis	0.43 [0.19, 0.95]	0	5	280	12 (7–100), 12.8%
CMV infection	0.64 [0.46, 0.88]	25	7	382	8 (5–25), 33.0%
Rebound CMV disease	0.77 [0.41, 1.41]	16	41	121	NS
Rebound CMV infection	0.77 [0.46, 1.27]	7	5	232	NS
VZV	0.13 [0.03, 0.55]	0	9	482	8 (2–33), 9.6%
Rebound VZV	3.19 [1.16, 8.78]	0	5	212	8 (5–50), 16.1%
Antiviral prophylaxis versus placebo/pre-emptive therapy in the post-engraftment period of HSCT					
HSV disease	0.26 [0.14, 0.49]	14	4	230	4 (3–6), 40%
HSV infection	0.31 [0.15, 0.61]	66	9	764	4 (3–8), 34.5%
Rebound HSV disease	9.52 [1.24, 73.07]	0	3	122	8 (4–25), 13.3%
Rebound HSV infection	6.69 [1.53, 29.28]	4	4	204	9 (6–25), 11.8%
CMV disease	0.42 [0.29, 0.62]	54	7	962	12 (9–20), 16.7%
CMV pneumonitis	0.46 [0.29, 0.74]	0	6	778	14 (9–33), 13.5%
CMV infection	0.53 [0.39, 0.73]	57	9	1071	4 (3–9), 45.7%
Rebound CMV disease	2.01 [1.00, 4.04]	0	5	624	NS
Rebound CMV infection	3.33 [0.54, 20.51]	0	4	296	NS
VZV	0.18 [0.08, 0.42]	0	8	713	12 (9–20), 9.3%
Rebound VZV	3.00 [1.24, 7.28]	0	4	230	10 (5–33), 15.6%
Antiviral prophylaxis versus placebo for intensive chemotherapy					
HSV disease	0.10 [0.04, 0.22]	0	5	305	3 (2–4), 37.4%
HSV infection	0.09 [0.04, 0.21]	0	5	305	2 (1–3), 47.1%
Rebound HSV disease	0.58 [0.32, 1.07]	0	3	108	NS
Rebound HSV infection	0.61 [0.19, 1.92]	0	2	79	NS
CMV infection	2.48 [0.38, 16.13]	0	2	136	NS

a Number needed to treat (NNT) for viral rates and number needed to harm (NNH) for rebound effect with event rate (ER) in the control group for NNT and event rate with intervention for NNH.
b Non-significant result, NNTs not calculated.

exposure to acyclovir in the past, out of 19 patients in one trial[89], and no resistant isolates were described in one trial.[106]

4. Discussion

Antiviral prophylaxis during the pre-engraftment phase of allogeneic or autologous HSCT reduced morbidity without improving the overall survival. A gain was observed with regard to HSV disease, representing mainly mucocutaneous disease, although HSV, CMV and VZV sub-clinical infections were significantly reduced as well. Patients were selected for prophylaxis based on positive serology for HSV and the drug used was nearly always acyclovir. The patients treated with intensive chemotherapy for acute leukaemia or high-grade lymphoma, similarly gained a significant reduction in HSV disease and infection rates, with no improvement in survival. The NNT for HSV disease in both scenarios was low, in the range of 2–4 patients (control event rate (CER) 61.9% in the pre-engraftment phase and 37.4% in chemotherapy patients).

During the post engraftment period of allogeneic HSCT, antiviral prophylaxis significantly improved overall survival, with a NNT of 12 patients (7–50, CER 39.4%). Significant reductions were seen with regard to HSV, CMV and VZV diseases and infection rates. Acyclovir, ganciclovir and maribavir were assessed for this indication. The patients were selected for prophylaxis based on positive CMV serology and prophylaxis was continued usually for 100 d post-transplantation. Adverse effects were more frequent with prophylaxis, mainly on account of neutropaenia caused by ganciclovir. More herpesvirus infections occurred after cessation of prophylaxis compared to placebo, but did not supersede the benefit observed during therapy. Resistance development was addressed in 8 trials, of which no resistant isolates were reported in 6.[85,89,92,102,105,106]

We compiled the trials according to the clinical scenario rather than the targeted virus, since in clinical practice we do not aim to prevent HSV or CMV infection, but rather to improve overall patient outcomes. We selected to base our analysis primarily on clinical outcomes; overall mortality, since herpesvirus infections may indirectly affect survival,[110,111] HSV and CMV clinical diseases. Despite the mix of different patients, HSCT types, chemotherapy regimens and viral target of the study, heterogeneity was null in most comparisons. When present, heterogeneity resulted from differing degrees of benefit rather than divergent results. Funnel plot analysis was limited by the small number of studies for each analysis, but small study's effect could be seen for viral-related out-

Table 3 – Further randomised controlled trials needed to answer unsolved questions (may be online only).

Post-engraftment

- Efficacy and duration of prophylaxis among lower-risk HSCT recipients (autologous HSCT, reduced intensity/non-myeloablative conditioning regimens)
- Duration of prophylaxis among higher-risk HSCT recipients (haploidentical HSCT, mismatched related or unrelated, T-cell depletion and GVDH)
- The benefit of antiviral prophyalxis in high-risk subgroups of patients that were not previously assessed (e.g. late-acute and chronic GVHD)
- The efficacy of prophylaxis for HSV-positive or VZV-positive, CMV-seronegative recipients
- Head to head comparison of acyclovir and antivirals with enhanced coverage for CMV (ganciclovir and maribavir)
- Pre-emptive treatment for CMV, with or without acyclovir prophylaxis
- Long-term prevention strategies for VZV disease

Pre-engraftment/chemotherapy

- The effect of antiviral prophylaxis on mucositis in general and overall patient morbidity
  Other setting
- The efficacy of antiviral prophylaxis versus placebo with the administration of monoclonal antibodies (rituximab, alemtuzumab, etc.)

comes both pre- and post-transplantation, pointing at the possibility that small studies that did not find a reduction in the incidence of the targeted virus remained unpublished.

Oral mucositis affects most patients during the neutropaenic phase of HSCT conditioning and incurs significant patient morbidity.[112,113] HSV is responsible for about 1/4 of mucositis episodes, albeit the more severe cases.[114–116] Antiviral prophylaxis reduced HSV mucositis in the setting of HSCT pre-engraftment and intensive chemotherapy, but the overall morbidity related to mucocutaneous disease among these patients has not been assessed. HSV may rarely cause severe pneumonitis (reported in a single trial in our review[89]); however, current data does not point towards a benefit with prophylaxis on severe infections and mortality during these phases. Post-engraftment, impaired cell-mediated immunity exposes patients to severe herpesvirus-related disease,

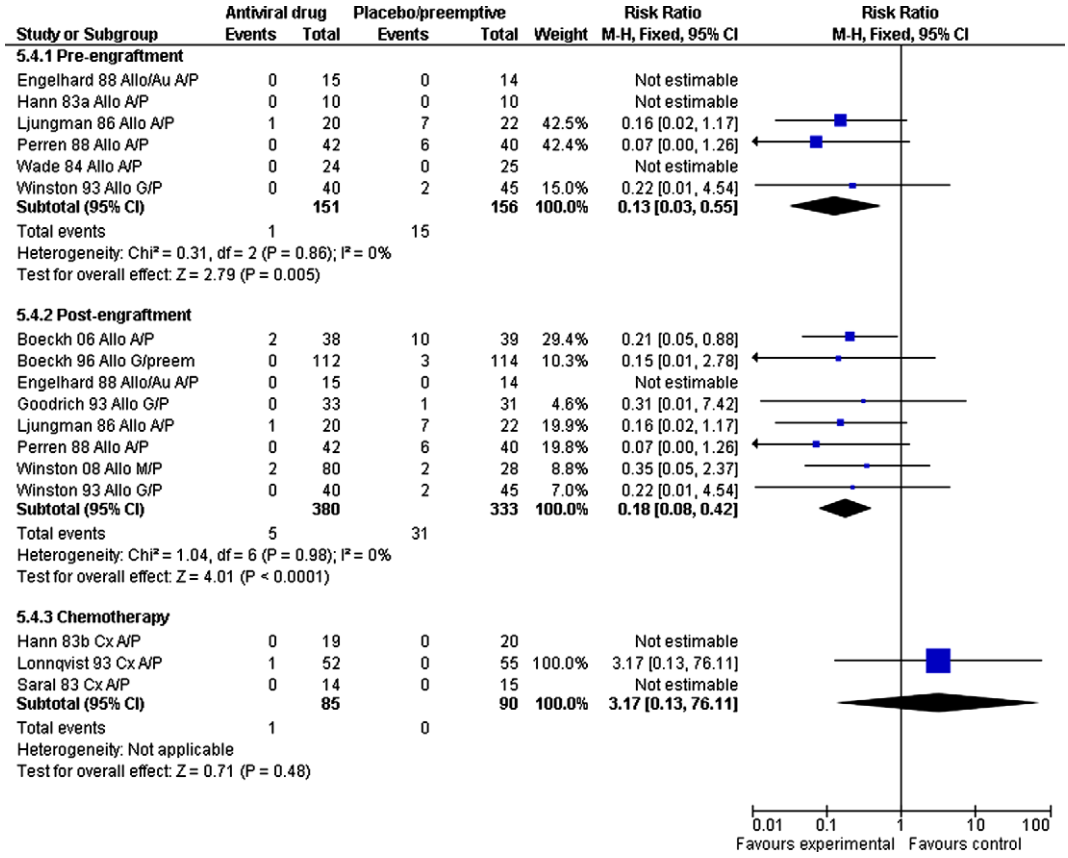


Fig. A1 – VZV disease for antiviral prophylaxis versus placebo/no treatment or pre-emptive treatment. Abbreviations as for Fig. 2. RR scale range 0.002–500.

Table A1 – Definitions of herpesvirus infection and disease in the individual trials.

Study ID	HSV disease definition	HSV disease occurrence in results	HSV infection definition	CMV disease definition	CMV infection definition	VZV disease definition
Anderson 1984	Oral lesions (coldsores, ulceration,stomatitis) ± culture	Oral lesions in all (accompanied by fever or pharyngitis/laryngitis in one patient each)	Oropharyngeal culture	Not reported	Not reported	Not reported
Bergmann 1995	Oral lesions (including herpes labialis, intraoral ulcers, acute necrotising ulcerative gingivitis) + viral culture or history of recurrence	Oral lesions	Oropharyngeal culture	Not reported	Not reported	Not reported
Boeckh 1996	Not reported	Not described	Oropharyngeal culture	Demonstration of CMV by biopsy specimens from visceral sites by culture or histology or if CMV was detected in culture or direct fluorescent antibody stain in BAL in the presence of new or changing pulmonary infiltrates	Positive antigenaemia or viraemia or detection of CMV DNA by PCR	Not given
Boeckh 2006	Not reported	Probably oral disease confirmed by culture	Culture from throat washing, urine or mucocutaneous lesion	Not reported	Not reported	Signs and symptoms of herpes zoster + viral culture/histopathology from lesions
Boeckh 2008	Not reported	Not reported	Not reported	Not reported	Detection of CMV DNA by PCR	Not reported
Burns 2002	Not reported	Not reported	Not reported	Signs/symptoms of disease in conjunction with culture of CMV from visceral tissue or cerebrospinal fluid, or pathologic changes of CMV in biopsy tissue	Positive antigenaemia	Not reported
Engelhard 1988	Ulcerations with positive culture or characteristic vesicles on the lips	Oral lesions	Oropharyngeal culture or serology	Not reported	Urine CMV excretion	Classical clinical picture
Gluckman 1983	Oral ulceration + culture	Oral lesions in all, some also had fever	Oropharyngeal culture or serology	One of fever, pancytopaenia, hepatitis, pneumonitis + isolation from blood or lung biopsy material	Urine, blood and throat cultures	Not reported
Hann 1983a	Mucosal ulceration or vesiculation from which the virus was isolated	Oral lesions in all, one patient had also fever and genital lesions + positive urine culture	Urine and oropharyngeal cultures	Typical clinical picture (hepatitis, pneumonia, falling blood counts or fever) plus serology (X4)	Urine, oropharyngeal cultures and serology	Typical clinical picture plus positive culture

(*continued on next page*)

Table A1 – continued

Study ID	HSV disease definition	HSV disease occurrence in results	HSV infection definition	CMV disease definition	CMV infection definition	VZV disease definition
Hann 1983b	Mucosal ulceration or vesiculation from which the virus was isolated	Oral lesions in all, in addition there were nasal lesions (2 patients), oesophageal ulceration (3 patients) and pneumonits (1 patient)	Urine and oropharyngeal cultures	Typical clinical picture (hepatitis, pneumonia, falling blood counts or fever) plus serology (X4)	Urine, oropharyngeal cultures and serology	Typical clinical picture plus positive culture
Liesveld 2002	Mucositis + pharyngeal viral culture	No HSV disease found	Pharyngeal culture	Not reported	Not reported	Not reported
Lonqvist 1993	Positive culture or immunofluorescence from vesicular material or positive serology	Probably oral disease confirmed by culture	Culture or serology	Not reported	Culture and serology	Not reported
Ljungman 1986	Mucocutaneous lesions + virus isolation or immunofluorescence	Probably mucocutaneous disease only	Culture of throat washings, blood and urine or serology	Serology or urine/blood culture	Serology or urine/ blood culture	Clinical varicella or herpez zoster ± virus isolation or immunofluorescence
Ljungman 2002	Not reported diagnosis ± laboratory confirmation	Not described	'Virologically confirmed'	Clinical picture (pneumonitis, retinitis, hepatitis, GI disease) and biopsy proof of CMV. Presumptive CMV disease: clinical picture + CMV in blood	Culture of urine or blood, antigenaemia or PCR	Clinical
Perren 1988	Not reported	Probably oral disease only	Culture of blood, urine, throat washings and mouth swabs	Not reported	Culture taken from blood, urine, throat washings and mouth swabs, or early antigen detection in tissue culture	Typical clinical picture supported by virus isolation where appropriate
Pineiro 1977	Not reported	Not reported	Not reported	Not reported	Blood culture or antigenaemia	Not reported
Prentice 1997	Not reported	Not described	Not reported	Clinical disease + Isolation of CMV fron any body fluid (blood, urine, throat washings, BAL) or tissue. Pressumptive disease: viraemia + clinical hepatitis or CMV syndrome	Isolation of CMV fron any body fluid (blood, urine, throat washings, BAL) or tissue	Not reported

Saral 1981	Recovery of the virus from an acute mucocutaneous lesion (ulcer or vesicle)	Oral lesions in all, genital disease also in one patient	Cultures of throat washings and urine	Symptoms + culture (taken from urine and throat washings)	culture taken from urine and throat washings	Not reported
Saral 1983	Recovery of the virus from an acute mucocutaneous lesion (ulcer or vesicle)	Oral lesions in all	Cultures of throat washings and urine	Not reported	Culture taken from urine and throat washings	Not reported
Shepp 1985	Mucocutaneous lesions + recovery of virus	Oral lesions in all, genital disease also in one patient	Cultures of urine, mouth and lips	Not reported	Not reported	Not reported
Shepp 1987	Mucocutaneous lesions + recovery of virus	Oral lesions in all	Cultures of urine, mouth and lips	Not reported	Not reported	Not reported
Wade 1984	Mucocutaneous lesions + recovery of virus	'Mucocutaneous'	Cultures of urine and oropharynx	Not reported	Not reported	Not reported
Warkentin 2002	Mucosal ulceration or vesiculation from which the virus was isolated symptoms + virological confirmation	Oral lesions	Oropharyngeal culture	Clinical signs and symptoms with virological confirmation	'virological confirmation'	Clinical signs and
Winston 1993	Not reported	'Localised infections'	Culture, unspecified	Clinical signs and symptoms with virological confirmation	Culture from any site, serology, inclusion bodies in tissue specimen	Not reported
Winston 2003	Mucocutaneous lesions + recovery of virus	Oral and genital lesions	Culture of blood, urine, throat, skin or any other	Clinical signs and symptoms with virological confirmation	Positive culture from blood, urine, throat, skin or any other	Mucocutaneous lesions + recovery of virus
Winston 2008	Not reported	Localised infections	Not reported	Clinical signs and symptoms with virological confirmation	Positive antigenaemia or PCR	Not reported

mainly CMV and VZV diseases. Indeed prophylaxis at this stage significantly reduced mortality, concurrently with all herpesvirus disease rates.

We intended to assess antiviral prophylaxis among other haematological cancer patients, including those with chronic lymphocytic leukaemia (CLL) and patients receiving monoclonal antibodies, where the question of antiviral prophylaxis frequently arises. No trial assessing the efficacy of antiviral prophylaxis (versus placebo/no treatment) was identified. A single trial compared valganciclovir and valacyclovir among patients with CLL treated with alemtuzumab.[48] Mortality rates were not reported in this trial and CMV disease rates were significantly lower with valganciclovir. Given improved survival with antiviral prophylaxis among post-engraftment HSCT recipients, the question of antiviral prophylaxis for other haematological cancer patients in whom the main immune deficit is cellular, remains highly pertinent and unanswered.

Further gaps in evidence and limitations of our analysis are apparent. The need for prophylaxis among lower risk HSCT recipients (autologous and non-myeloablative allogeneic HSCT) was not assessed. Non-myeloablative HSCT recipients were included in a single trial[102] (21–39% of patients included). Infections may occur later with non-myeloablative regimens and their incidence is affected by co-administration of alemtuzumab and other T-cell depletion.[117–121] Similarly, we could not assess prophylaxis in higher-risk patient subgroups, such as those with mismatched HSCT, T-cell depletion and GVDH. Although included in existing trials (Table 1), neither subgroup analysis nor meta-regression was possible due to the small number of studies included in each comparison. We could not determine the comparative benefit of different antiviral drugs. Acyclovir is more effective against HSV and gancyclovir is more effective against CMV, as apparent in our analyses. However, both acyclovir and ganciclovir reduced mortality following HSCT. Finally, we were not able to show how antiviral prophylaxis prevents mortality. The impact on mortality and CMV disease in the post-engraftment setting suggests a causal relation, but indirect effects cannot be ruled out. We attempted to extract data on bacterial and fungal infections, but these were rarely reported and no differences were observed when reported (data not shown).

Further trials are needed to address the questions given in Table 3. Future trials should adhere to adequate allocation concealment.[122] The trials should report on overall disease rates, such as any mucositis, (in addition to virologically confirmed disease) to allow the appraisal of overall morbidity benefit.[123] Standard definitions and follow-up durations are needed for these trials, given the wide variability in outcome definitions of currently existing trials (Table A1). Resistance following treatment should be uniformly assessed.

Based on current evidence, antiviral prophylaxis should be administered to all CMV-seropositive HSCT recipients post engraftment. Since prophylaxis in this setting significantly reduces overall mortality, CMV, VZV and HSV disease rates, consideration should be given to the use of prophylaxis also for VZV-seropositive or HSV-seropositive (CMV seronegative) recipients, as well. These implications are in accordance with the current guidelines, although the recommendation for prophylaxis for CMV-seronegative recipients is variable in different guidelines.[4–8] The type and duration of prophylaxis, tailored to individual patient's risk, remain to be determined; currently acyclovir, ganciclovir and maribavir showed similar efficacy and prophylaxis was administered for 100 d post-engraftment or longer. During the pre-engraftment period and for patients undergoing intensive chemotherapy, antiviral prophylaxis does not reduce mortality and its effect on overall patient morbidity is unknown. Therefore, decisions can be made individually and prophylaxis may be withheld if the risk for adverse events or intolerance is significant.

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Conflict of interest statement

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Appendix

See Fig. A1 and Table A1.

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